

# Toxicology News

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## Clopidogrel is Thienopyridine Leader for Atherosclerosis

*By John M. Koerber*

**T**he management of cardiovascular atherosclerotic disease events (such as acute myocardial infarction and stroke) has significantly evolved over the last several decades. An improved understanding of the pathophysiological processes involved has led to the development of many new classes of medications.

Acute coronary syndromes such as unstable angina generally occur when there is a disruption of an atherosclerotic plaque. This disruption leads to a “snag” in the damaged blood vessel, which initiates a cascade of events, including platelet activation and further blockage of the damaged vessel. Ischemic stroke is thought to evolve in a similar fashion. Based on this model of atherosclerotic disease, the inhibition of platelet activation and/or function is a logical place to target new therapies.

### Thienopyridines introduced

In 1991, the Food and Drug Administration (FDA) approved ticlopidine, the first of a new class of antiplatelet agents called thienopyridines. Ticlopidine (Ticlid) interferes with platelet membrane function by inhibiting platelet-fibrinogen binding induced by adenosine diphosphate (ADP), which inhibits subsequent platelet interactions (1). It is currently approved to reduce the risk of thrombotic stroke in patients who experienced stroke precursors or a thrombotic stroke and for the prevention of subacute stent thrombosis in patients undergoing a stent placement (1). Unfortunately, ticlopidine is associated with life-threatening hematological side effects, including aplastic anemia and thrombotic thrombocytopenic purpura (TTP), and has been relegated to a second- or third-line agent.

In 1997, the second thienopyridine was approved. Clopidogrel (Plavix) is an irreversible in-

hibitor of ADP-induced platelet aggregation. It acts by direct inhibition of ADP binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex (2). Chemically it is methyl (+)-(*S*)- $\alpha$ -(2-chlorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridine-5(*4H*)-acetate sulfate (1:1).

Clopidogrel is rapidly absorbed after oral administration and can be taken without regard to meals. It is not active until metabolized by the cytochrome P450 system of enzymes. It has a half-life of about eight hours and is primarily metabolized by the liver.

Two recent articles have explored the possibility that patients whose 2CYP19 enzyme has reduced function have higher rates of cardiovascular events (3, 4). Polymorphism of the CYP3A4 gene has also been suggested as playing a role in clopidogrel failure (5). Except for medications that also increase the risk of bleeding, there are no known significant drug interactions with clopidogrel.

### Approved uses

Clopidogrel is currently FDA-approved for use in patients experiencing recent myocardial infarction (MI) or recent stroke, and patients who have established peripheral arterial disease (2). It has been shown to reduce morbidity and mortality in patients with stroke and acute coronary syndrome.

The American Heart Association (AHA) has issued clinical guidelines for its use in the treatment of acute coronary syndromes, ischemic stroke, and peripheral arterial disease (6–9).

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## Street Drugs BZP and TFMPP Can be Mistaken for Ecstasy

By Bophal Sarha Hang, Vito J. Rocco, and John Wilson

In May 2008, during the Detroit Electronic Music Festival, an 18-year-old African-American woman presented to a suburban Detroit emergency department. She had been out with friends and reported using cocaine and ecstasy a few hours prior to arrival. After ingesting three pills of what a dealer told her was ecstasy, she had a seizure that lasted approximately four minutes. On arrival, she was alert and oriented with a Glasgow coma scale of 15. She complained of a headache similar to migraines she had in the past. Physical examination was significant for dilated pupils (7 mm), high heart rate (91 bpm), tachypnea (22 breaths/min), and elevated blood pressure (140/80 mmHg). The patient was afebrile and otherwise appropriate during the exam. She had a medical history significant for migraines and chronic back pain, for which she was taking Abilify, Fioricet, and Xanax.

### Test results and treatment

Initial toxicological screening detected cocaine and cannabinoids in a urine sample. Laboratory results showed mild leukocytosis ( $13.4 \times 10^6/L$ ), hyponatremia (134 mg/dL), and hyperglycemia (142 mg/dL). Other laboratory findings were within normal limits. A head CT scan was negative for any intracranial process, and an ECG was unremarkable. Comprehensive toxicological screening confirmed the presence of 3,4-methylenedioxy-N-methylamphetamine (MDMA, commonly known as ecstasy), N-benzyl-piperazine (BZP), and 1-(3-trifluoromethylphenyl)piperazine (TFMPP).

In addition to treatment of her symptoms, the patient was given 1 gram of Dilantin for seizure prophylaxis. After several hours of observation, the patient was discharged in stable condition and advised to seek rehabilitation and counseling for substance abuse.

### Background

BZP and TFMPP belong to a family of drugs called piperazines, which were initially studied as antidepressants in the 1970s. When human studies found that their effects were similar to those of amphetamine, the development of piperazines as antidepressants was halted because of their potential for abuse (1).

Because of this similarity to amphetamine,

piperazine derivatives have gained popularity in some countries as supposed legal substitutes for ecstasy (2). Discussions on the legal status of piperazines are ongoing in many countries, including Canada and some European countries. To date, there are no international regulations on the use of BZP and TFMPP (3). In the United States, BZP and TFMPP were classified into Schedule I of the Controlled Substances Act in 2002, but the scheduling of TFMPP was later lifted, leaving it currently unregulated (4). Until recently, piperazines were legal to sell in the United Kingdom and New Zealand in herbal supplements and as “pep pills” advertised to mimic the euphoric and hallucinogenic effects of ecstasy (3, 5).

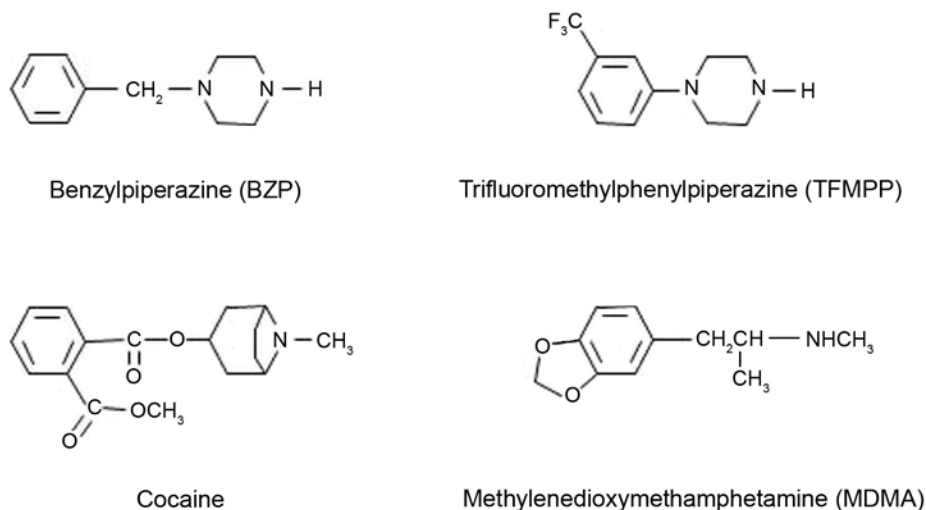
Street names for piperazine derivatives such as BZP and TFMPP include legal E, legal X, A2, and molly. Piperazine blends have also been found in combination with ecstasy or cocaine (6). These drugs represent a group of emerging designer drugs that may be wrongly diagnosed as amphetamine poisoning and may have increased risks when co-ingested.

### Discussion

This is the first case report of a seizure secondary to poisoning from the use of BZP and TFMPP in the United States. The patient was one of two who presented to the emergency department with poisoning related to BZP/TFMPP the weekend of the Detroit Electronic Music Festival. The timing suggests that they ingested a contaminated drug or that these party drugs were sold during the festival, which draws an international crowd, some of whom may have imported the drugs.

In the United Kingdom, Wood and colleagues reported a case of poisoning with 1-benzylpiperazine leading to seizure. However, to date there have been only a few case reports of poisoning related to BZP, and one death associated with combined ingestion of ecstasy and BZP (6–8). The combination of BZP and TFMPP has been detected in association with other similar psychoactive drugs in several fatalities (2, 3). Some studies have suggested that combining these drugs may increase their adverse side effects. Bauman et al. found that a dangerous drug–drug synergism occurred when piperazines were co-administered at high doses (6).

These drugs have narrow safety margins and are metabolized by cytochrome P450, which might result in increased risk of toxicity in those with poor cytochrome P450 metabolism. In addition, co-ingestion with cocaine and MDMA may increase toxic side effects (6, 9). In clinical trials, the adverse effects of benzylpiperazine were similar to those of amphetamines, and included including nausea, vomiting,



**Figure 1. Chemical Structures of BZP, TFMPP, Cocaine, and MDMA**

tachycardia, hypertension, anxiety, and agitation (1, 6, 9). A prospective study in New Zealand of BZP-based “herbal party pills” reported seizures in 15 patients, with two patients suffering status epilepticus and severe respiratory and metabolic acidosis. BZP appeared to produce toxic seizures in neurologically normal patients. Some studies have also suggested that BZP/TFMPP toxicity is greater in females (10).

Many clinicians are not familiar with the clinical presentations and toxic effects of these drugs, so it is important to raise clinical awareness of them. Management mostly consists of supportive care and observation.

### Analysis

Piperazines are readily analyzed by gas chromatography/mass spectrometry. Representative mass spectra can be seen at [www.dea.gov/programs/forensicsci/microgram/index.html](http://www.dea.gov/programs/forensicsci/microgram/index.html).

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## Clopidogrel

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### Coronary guidelines

MI patients are generally divided into two categories: those who experience an acute ST-elevated myocardial infarction (STEMI) and those who don't (non-STEMI, non-Q wave MI, or unstable angina). Treatment recommendations vary slightly between the categories.

Both groups of patients receive dual antiplatelet therapy with aspirin and clopidogrel unless there are special contraindicating circumstances. A loading dose of clopidogrel (300 mg in STEMI and 300–600 mg in non-STEMI) is recommended for most patients (except for STEMI patients more than 75 years old) (6, 7). Patients are then placed on a daily maintenance dose of 75 mg. The loading and maintenance regimen applies to both patients treated with an invasive strategy such as percutaneous coronary intervention and those treated conservatively (without stent placement).

The duration of clopidogrel therapy depends on many factors, including the management strategy, the type of stent placed, and the individual patient's bleeding risk. Patients managed conservatively are treated for one month to one year. Patients who receive a bare metal stent receive 75 mg daily for at least one month, whereas those who receive a drug-eluting stent may take the drug for a year or longer.

Current research in acute coronary syndrome is focused on clopidogrel dosing strategies and use in combination with agents such as bivalirudin.

### Non-coronary recommendations

The AHA guidelines strongly recommend a 75-mg daily dose of clopidogrel for the treatment of stroke patients (8). A similar dose is recommended for patients with peripheral arterial disease, although the evidence of its efficacy is not as strong as the evidence for aspirin (9). Dual antiplatelet therapy in stroke patients is highly discouraged because of the increased risk of bleeding.

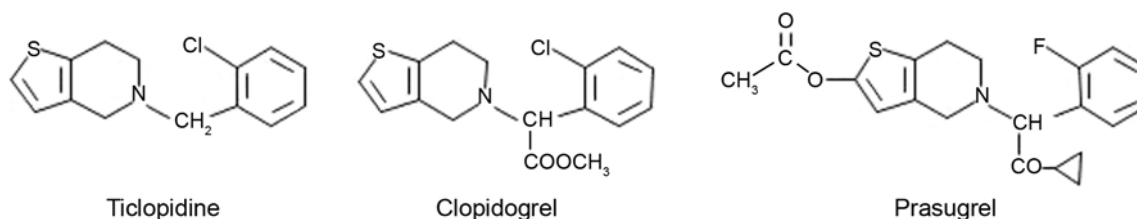
Although clopidogrel has by and large replaced

ticlopidine as the thienopyridine of choice, it has its share of adverse reactions. Not surprisingly, the most common side effect is bleeding, which can be as minor as a nosebleed or as major as intracranial hemorrhage. Major bleeding occurs in less than 1% of patients, although use in combination with aspirin increases this percentage. Other side effects include chest pain; flu-like symptoms; generalized pain; fatigue; edema; hypertension; headache; dizziness; abdominal pain; dyspepsia; diarrhea; nausea; increased lipid blood levels; muscle, joint, and back pain; depression; respiratory tract infection; difficulty breathing; rhinitis; bronchitis; coughing; rash; itching; and urinary tract infection. Clopidogrel has recently been associated with rare cases of TTP (10).

Although clopidogrel is still king, prasugrel is a third thienopyridine making its way through clinical trials. A study that compared the two directly found that acute coronary syndrome patients who underwent an intervention experienced significantly fewer ischemic events with prasugrel therapy, but had an increased risk of major bleeding, including fatal bleeds (11). Overall mortality did not differ between the groups.

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**Figure 1. Chemical Structures of the Principal Thienopyridines**

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### Ask an Expert

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## Soma Coma, or Carisoprodol Intoxication, Makes Comeback

*By Keenan Bora*

Meprobamate, a nonbenzodiazepine nonbarbiturate sedative-hypnotic, was first marketed in the 1950s as a muscle relaxant under the brand names Miltown and Equanil. In 1959, the prodrug for meprobamate, carisoprodol (Soma), was first described in a seminar at Wayne State University and marketed later that year (1). These medications were introduced at a time when phenobarbital was falling out of favor as a sedative-hypnotic and before the advent of benzodiazepines.

The first reports of meprobamate abuse and carisoprodol abuse surfaced within a few years of their introductions. The National Survey on Drug Use and Health estimated that 2.28 million U.S. residents 12 years and older have used carisoprodol nonmedically at least once. According to the American Association of Poison Control Centers, carisoprodol, as a single overdose agent, accounted for 3,536 reports in 2007 and, in combination with other drugs, 8,658 reports.

A schedule IV drug in 10 states, carisoprodol is one of 11 substances under observation by the Researched Abuse, Diversion and Addiction-Related Surveillance System, a project of the Rocky Mountain Poison and Drug Center that monitors prescription drug abuse and misuse. Carisoprodol is outlawed in Norway, and the European Medicines Agency has recommended that the marketing of all carisoprodol-containing products be suspended throughout Europe.

### Diagnosis

Meprobamate and carisoprodol act primarily through gamma-aminobutyric acid receptor-A (GABA<sub>A</sub>) activation and cell membrane hyperpolarization. After carisoprodol ingestion, the lab results and physical exam tend to be normal except for a profound central nervous system depression, known in many emergency departments as “Soma coma.” In coma patients, the drugs that toxicological tests must differentiate include benzodiazepines, atypical antipsychotics, antidepressants, antihistamines, barbiturates, and other nonbenzodiazepine nonbarbiturate sedative-hypnotics, including carisoprodol.

Patients who have ingested carisoprodol may have myoclonus that mimics serotonin excess (2). This condition is not seen with meprobamate. Carisoprodol intoxication tends to last less than 24 hours and then resolve with few side effects, although deaths have been reported. Drugs such as aripiprazole

and benzodiazepines may present similarly, but may have a much greater duration of action. Although patients have a relatively good prognosis with carisoprodol and meprobamate ingestion, morbidity and mortality are related to secondary complications such as aspiration and rhabdomyolysis.

### Detection and metabolism

Laboratory quantification of carisoprodol dates back to 1959, when the original paper described a colorimetric method (1): "The color produced on reacting carisoprodol in chloroform solution with p-dimethylamino benzaldehyde and antimony trichloride serves as an excellent method for determination of this compound, and can be applied to the estimation of carisoprodol in body fluids."

In therapeutic dosing, peak plasma concentrations occur within one hour and should be less than 5 mg/L. Meprobamate levels should peak in three to four hours and be less than 5 mg/L. Death has been reported at 4.5 hours with carisoprodol and meprobamate concentrations of 36 mg/L and 15 mg/L, respectively (3).

Although genetic variants of CYP2C19 can alter the timing of metabolism, the meprobamate concentrations usually exceed the carisoprodol levels by 2.5 hours post-ingestion (4). In a small percentage (2–3%) of the population who cannot metabolize carisoprodol, the half-life is six hours or more. Oral contraceptives can also affect metabolism time (5). Gas chromatography/mass spectrometry methods for determining post-mortem concentrations of meprobamate in overdose have been described (6). Liquid chromatography/mass spectrometry methods have been described in a variety of animal models (7).

In the undifferentiated, unconscious overdosed patient, obtaining parent and metabolite concentrations and the time of ingestion might help in predicting the patient's course. In addition, negative levels of both drugs would encourage physicians to look for other causes of a patient's coma while continuing the supportive care that is the mainstay of treatment.

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## Hepatotoxicity Makes Herbal Supplement Kava Dangerous

*By Amitava Dasgupta*

Kava is an herbal sedative prepared from a South Pacific plant (*Piper methysticum*) that has purported anti-anxiety or calming effects. Kava drink is prepared by mixing fresh or dried root with cool water or coconut milk. Kava is available from a variety of manufacturers; Kavatro is a brand found in many health-food stores.

Kava is reported to produce a mild euphoria characterized by happiness, lively speech, and increased sensibility to sound. Its neurological effects are attributed to a group of substituted dihydropyrone called kava lactones. The main bioactive compounds include yangonin, desmethoxyyangonin, 11-methoxyyangonin, kavain, and dihydroxykavain. These components are present in the lipid soluble kava extract or kava resin (1).

Once thought to be safe, the latest findings now indicate that kava's toxicity outweighs its benefits.

### Sedative effects

Kava is one of the best-selling herbal supplements in the United States. The standard dose is 100 mg of an extract of 70% kava lactones taken two or three times daily, which is equivalent to 140–210 mg per day of active substance. Scherer reported a study involving 50 patients suffering from anxiety of

nonpsychotic origin who took kava (2). Forty-two patients experienced a significant response, which led the author to conclude that kava extract is an effective alternative to antidepressants and tranquilizers in anxiety disorder.

Pittler and Ernst performed a systematic review and meta-analysis (3). All seven clinical trials reviewed found that kava was superior to placebo. The meta-analysis of three studies suggested that kava significantly reduced the patient's scores on the Hamilton Rating Scale for anxiety compared with placebo. The mechanism of the anxiolytic effect of kava is unclear due to conflicting reports regarding kava's effect on gamma-aminobutyric acid receptors.

### Toxicity

Dermatological effects have been reported following kava use. Chronic ingestion may cause yellowing of the skin, hair, and nails that is reversible upon discontinuation. A 70-year-old man who took kava products for anxiety for two to three weeks experienced itching several hours after exposure to sun. Erythematous infiltrated plaques then developed on his face, chest, and back. A 52-year-old woman presented with papules and plaques on her face, arms, back, and chest after taking kava products for three weeks. In both cases, biopsies revealed lymphocytic infiltration of the dermis with destruction of the sebaceous glands (4).

Kava has also been shown to have additive effects with central nervous system depressants. A patient who was taking alprazolam (Xanax), cimetidine, and terazosin became lethargic and disoriented after ingesting kava (5).

Long-term use of kava can cause liver toxicity. Regular consumption is associated with increased concentrations of gamma-glutamyltransferase (GGT), suggesting potential hepatotoxicity. Escher et al. described a case in which kava use was associated with severe hepatitis in a 50-year-old man who took large daily doses for two months (6). Liver function tests showed 60-fold increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). A blood test was negative for hepatitis A, hepatitis B, hepatitis C, cytomegalovirus, and human immunodeficiency virus. The patient eventually received a liver transplant. Humberston et al. also reported a case of acute hepatitis induced by kava (7).

### Mortality

Use of kava has been associated with fatalities. Although kava was once considered a safe herbal sedative, recent research clearly indicates that its toxicity has been underestimated. In January 2003, kava extracts were banned in the entire European Union

and Canada. The U.S. Food and Drug Administration has strongly cautioned the general public against using kava. There are at least 11 cases of serious hepatic failure and four deaths directly linked to kava extract consumption and 23 reports indirectly linking kava with hepatotoxicity (8). However, for centuries South Pacific islanders have consumed aqueous extracts of kava in ceremonies without serious toxicity.

Cote et al. observed that there was a significant difference between the kava lactones in aqueous extracts compared with those in commercial organic extracts (9). Commercial extracts' inhibition of liver enzymes CYP3A4, CYP1A2, and CYP2C19 was more pronounced compared with traditional aqueous extracts. The authors concluded that the variation in health effects reported for kava extracts may be related to different protocols of preparation. Kava's hepatotoxicity and the deaths associated with its use mean that it represents a significant but under-recognized danger.

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## FDA Issues Update on Genetic Testing and Antiepileptics

By Alan H.B. Wu

In the December 2008 issue, Dr. Bonny Lewis Bukaveckas reported on the potential need to perform genetic testing for HLA-B\*1502 before prescribing the antiepileptic drug carbamazepine. In certain ethnic populations, particularly Han Chinese, Filipinos, Malaysians, South Asian Indians, and Thais, severe cutaneous reaction syndromes (SCARS) can occur in individuals with this genotype.

This concern prompted the Food and Drug Administration's Center for Drug Evaluation and Research (CDER) to change carbamazepine's prescribing information in December 2007 to state that "at risk populations should be screened for the presence of HLA-B\*1502."

In November 2008, the CDER announced that it was also investigating preliminary data regarding similar SCARS risks of the other popular anti-convulsants phenytoin and fosphenytoin for patients with this genotype (1, 2). The CDER recommended that "until the evaluation is complete," healthcare providers should be "aware of the risks" and "avoid phenytoin and fosphenytoin as alternatives to carbamazepine in patients who test positive for HLA-B\*1502."

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Readers are invited to submit questions they would like answered by an expert. An e-mailable PDF copy of this newsletter is available: [cftnews@aacc.org](mailto:cftnews@aacc.org).

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