Debate Continued on Best Agent for Coke Withdrawal

BY RICK MCGUIRE

LOS ANGELES — As recently reported in this newspaper, UCLA researcher Dr. Forest Tennant believes the antiflu agent amantadine is an effective therapeutic agent for cocaine withdrawal (MT, May 21). In fact, he contended, it is more effective than either bromocriptine or desipramine—drugs about which similar claims have been made in recent years.

Dr. Tennant's data are still several months from publication. Meanwhile, other cocaine researchers are defending their use of desipramine and bromocriptine.

"I do argue with Dr. Tennant's view of desipramine," said Dr. Frank Gawin director of the stimulant abuse center at Yale. "We have in fact found that the drug is very effective when given for 12-26 weeks at dosages of 200-400 mg." He added, "In Dr. Tennant's [desipramine] study, he used much lower doses for only three weeks."

In his own studies at Yale, Dr. Gawin found that desipramine was no more effective than placebo until about the 17th day, then from that point on "the desipramine patients did much better."

Likewise, Dr. Charles Dackis, a director of neuropsychiatric evaluation at Fair Oaks Hospital, Summit, N. J., disagrees with Dr. Tennant's arguments against bromocriptine. "I think Dr. Tennant saw the side effects that he did with bromocriptine because he was using two and a half times the dosage that we use here at Fair Oaks," said Dr. Dackis. "We have never seen the side effects he reported.

"Occasionally, we'll find a patient who experiences mild dizziness, but we have seen no syncope or nausea at all," he said.

The Fair Oaks regimen, according to Dr. Dackis, is 0.625 mg three times a day for two weeks. "We may increase the dosage after the [the patient's brain] receptors have been desensitized to the drug, but even then we will rarely go higher than a 1.25 mg dose.

"I think our work suggests that cocaine addicts have supersensitized dopamine receptors and I just don't think they can realistically be expected to handle the dosage of bromocriptine that Dr. Tennant has been administering," he said.

Although two weeks is the typical regimen, Dr. Dackis noted that "30 percent of patients require longer trials," with a few receiving bromocriptine for up to nine months. He also expressed two serious concerns he has regarding the use of amantadine, both having to do with the drug's mechanism.

"We were first led to use bromocriptine because patients were low in dopamine. Bromocriptine, we thought, would act as a dopamine replacement in these patients," he said. "My concern with amantadine is that in releasing the patient's own stores of dopamine, might this not actually further deplete their [dopamine] stores? I have suggested to Dr. Tennant that he check the prolactin levels in his amantadine patients to see if indeed they are becoming further dopamine depleted."

However, Dr. Dackis said his biggest concern with amantadine is that "it may in and of itself be euphorigenic."

That possibility also bothers Dr. Gawin, who notes that there have been "scattered reports" of abuse linked to amantadine. Dr. Tennant begged the question slightly by pointing out that his patients never receive more than a two-day supply of amantadine at a time. Moreover, what follow-up data he does have suggest that most patients remain free of cocaine after three weeks of amantadine therapy. Counseling then continues and patients are monitored by urinalysis.

Said Dr. Gawin, "I am very glad that Dr. Tennant has done the comparison study of amantadine and bromocriptine.

According to Dr. Tennant, on an outpatient basis there is no doubt that amantadine is the better pharmacologic agent. "You've got to pick a drug that will not cause major problems if the patient takes cocaine on top of it," he said. "This has been a problem with bromocriptine. When taken with cocaine, there have been tremendous side effects. However, I have seen no side effects at all when using amantadine, even if the patient uses cocaine with it."

Upon consideration, Dr. Tennant allowed, "If the patient is hospitalized, then I think a doctor can choose amantadine or bromocriptine, whichever they're more comfortable with. However, on an ambulatory basis, I think amantadine hydrochloride is the most biocompatible and safest drug available."

Added Dr. Gawin, "What we're going to need now are studies following [amantadine] patients out to about 12 weeks. If indeed there is no need for continuing [pharmacologic] therapy beyond 21 days, then that's fine.

"But I suspect there will be a need for further therapy and eventually we may see patients started on both amantadine and desipramine. Amantadine will carry the patient for those first 17 days until the desipramine kicks in. Then therapy can be continued for from 12-26 weeks."

"I think from all of this it's clear that we now have several agents showing varying degrees of success in treating cocaine addiction," said Dr. Gawin. "So, it does look like pharmacology will play an important role in helping get people off of cocaine. Exactly what that role will be is yet to be seen."

For Infections of Urinary Tract, Choice is Clear

BY LIZA GALIN

AMSTERDAM — Advances in the treatment of urinary tract infections were the focus of a recent international symposium here.

Professor Fritz H. Schröder, chief of urology in the Faculty of Medicine at Erasmus University, Rotterdam, noted at the outset that urinary tract infection (UTI) is among the most common maladies encountered by family practice physicians—a fact that is not always appreciated.

Members of the symposium generally agreed that nitrofurantoin continues to be a most effective drug in the treatment of acute, uncomplicated UTI 30 years after its introduction.

During the past three decades, nitrofurantoin has undergone constant clinical evaluation. "The important thing," said Dr. Joseph Corriere, Jr., professor and director of urology at the University of Texas Medical School, Houston, "is that a drug that has been around for 30 years continues to have the same efficacy and the same ability to work as any of the new drugs [and] at a cheaper price. New drugs come out, cost a lot of money, and become resistant right away. That doesn't happen with nitrofurantoin."

Nitrofurantoin in macrocrystal form (Macrodantin, Norwich Eaton) was reported to meet several important criteria for the treatment of uncomplicated UTI. It is an antibacterial drug specific for the urinary tract. It is orally administered, readily absorbed, rapidly excreted in the urine, where it is highly soluble, and has a short half-life. It is effective in a wide range of patients. It has relatively few side effects. And resistance to it has not been reported. The high rates of recurrence of UTI are due to factors other than antibacterial treatment, urologic authorities agreed.

"I think the one thing this drug has done is [that it has] stood the test of time," said Dr. Corriere. He attributed nitrofurantoin's utility, in part, to the fact that it does not substantially affect bowel or vaginal flora. "There's been minimal, if any, change at all in the sensitivity pattern of nitrofurantoin over the years," said Dr. Corriere. It is usually active against Escherichia coli, enterococci, and Staphylococcus aureus.

The problems with the more modern antibiotics, according to Dr. Corriere, is that they are too expensive and too high-powered, and are associated with certain toxicity problems. "You're taking a sledge hammer to kill a fly," he said. Although the sulfa drugs are cheap, he said, they can cause skin rashes, and some oral penicillin derivatives commonly cause diarrhea and vaginitis. "Many of those drugs have high blood levels that kill the flora of the colon and can instigate another infection from other bacteria in the colon. That cannot happen with a drug like nitrofurantoin macrocrystals, which work only in the urinary tract."

The most serious adverse reactions to nitrofurantoin are peripheral neuropathy, pulmonary infiltration, hematological reactions, and hepatic reactions. Results of a Norwich Eaton data-base study on adverse reactions to nitrofurantoin indicate that their calculated incidence is small—the most frequent side effects are anorexia, nausea, and emesis.

According to Professor P. F. D'Arcy, head of pharmacy and dean of the Faculty of Science at Queen's University, Belfast, Northern Ireland, nitrofurantoin's interactions with other drugs are trivial.

The key to UTI therapy during pregnancy, said Dr. Peggy J. Whalley, professor of obstetrics and gynecology at the University of Texas Southwestern Medical School, Dallas, is prevention. Most of the women who develop acute symptomatic UTI during pregnancy belong to a small (2-10%) group of patients who can be identified at their first prenatal visit as having asymptomatic bacteriuria (ASB). "Once identified, pregnant women with proven ASB should be treated with antimicrobial agents and then monitored for recurrent bacteriuria," said Dr. Whalley. Studies at Parkland Memorial Hospital in Dallas indicate that when a 100-mg bedtime dose of nitrofurantoin macrocyrstals is given for 10 days, no adverse fetal affects are detected and maternal side effects are minimal.

Professor D'Arcy noted that although nitrofurantoin crosses the placental barrier, it does so to such a limited extent that fetal toxicity is very unlikely. "The risk-to-benefit ratio is very much on the side of nitrofurantoin crystals when needed to treat bacteriuria during pregnancy," he said. The drug is contraindicated in pregnant women at term and in infants under one month of age because of the possibility of hemolytic anemia due to immature enzyme systems.

Pulmonary Emboli Yield to r-TPA

BY LAWRENCE PRESCOTT, PH.D.

ATLANTA — Pilot studies suggest that recombinant tissue plasminogen activator (r-TPA) may provide the physician with a safe and effective method of rapidly lysing pulmonary emboli, according to Dr. Samuel Z. Goldhaber, assistant professor of medicine at Harvard Medical School.

Dr. Goldhaber told the American College of Cardiology meeting here that lytic therapy is rarely employed for primary dissolution of clots because of the possibility of major bleeding. Heparin is relied upon for secondary prevention.

In the Harvard trial, 18 of 19 patients receiving intravenous r-TPA had angiographic evidence of clot lysis. In 16 of the 19, lysis was considered particularly successful. There was a 43% reduction in the average qualitative score of the pulmonary emboli; the score was 6.1 before treatment, and 3.4 after. Major bleeding was held to a minimum, reflecting a 35% reduction in average plasma fibrinogen following administration of r-TPA, reflecting a degree of systemic fibrinolysis.

One patient had pericardial tamponnade. Eleven had minor oozing from venipuncture sites, easily controlled with manual pressure. Four had a hematoma at the femoral venous sheath site.

In correlative European trials employing heparin as the chief agent to manage pulmonary embolism, only 4% of patients had significant clot dissolution.

All patients in the Harvard study were 18 years of age or older. Exclusion criteria included symptoms of pulmonary embolism for more than five days, surgery within the prior week, active internal bleeding in the last three months, stroke, or similar disorders.

Results Analyzed

Patients were given a continuous intravenous infusion of r-TPA (50 mg) over a two-hour period. Then angiograms were carried out. Those in whom lysis occurred were returned to routine care. Those without evidence of lysis were given an additional 40 mg r-TPA over a four-hour period. After angiograms, the trial ended.

The angiograms were coded and analyzed by a panel of at least three investigators. On pretreatment angiograms, nine patients had massive pulmonary emboli, encompassing the entire lung. Four were graded large, affecting two lobes; four were moderate, in only one lobe, and two were graded as pulmonary hypertension.