National Alliance of Methadone Advocates

435 Second Avenue
New York, NY 10010
Voice/Message/Fax
(212) 595-NAMA

Education Series Number 5.3
February 2001 (Revised)

Basic Pharmacology: How Methadone Works?

Drugs and Conditions That Impact On the Action of Methadone

by

J.T. Payte, Jeffrey Smith and Joycelyn Woods

Methadone Metabolism

Methadone was once considered to be pretty much the same for every patient. Thus, it was believed that narcotic blockade began at 60 mg/day for about 90% of the patients an adequate dose occurred at 80 mg/day. The measuring of serum methadone levels have shown that metabolism can vary significantly for many patients. In addition to methadone metabolism there are a variety of conditions and medications that can impact on the effectiveness of methadone (Leavitt, Shinderman, Maxwell, Eap, and Paris, 2000.)

1. Narcotic Antagonists and Agonist-Antagonists Drugs

An important property of all narcotic antagonists is that anyone dependent on any opiate, including methadone patients will be extremely sensitive to t

J. Thomas Payte, M.D. is Medical Director and Founder of Drug Dependence Associates in San Antonio, Texas, Chair of the Maintenance Medications Committee of the American Society of Addiction Medicine and a member of NAMA's Advisory Board.

Jeffrey Smith, Ph.D. has a degree is central nervous system pharmacology.

Joycelyn Woods, M.A. is President of NAMA. Her degree is in neurological psychology and she had done brain mapping of opiate receptors and published one of the early papers on it.

hem (Cooper, Bloom and Roth, 1991; Gilman, Rail, Niles and Taylor, 1990). These actions occur directly at the opiate receptor. Some of the new analgesics are mixed agonist-antagonists drugs which have been developed to reduce their addiction potential. For a non dependent person these medications are pain killers, however for methadone patients, or anyone

2. Aberrant Metabolizers, Alcoholism and Liver Disease

It is estimated that about 5% of methadone patients are what is called aberrant metabolizers (Payte and Khuri, 1992). Each time methadone passes through the liver some is lost. For the average metabolizer the loss is minimal but for fast metabolizers the loss can be immense. Liver disease and alcoholism can cause a reduction of the liver's ability to perform normal metabolic functions, resulting in aberrant metabolism. This condition is very difficult to correct and the only way to help the liver would be to eat a low fat diet to allow the liver to rest while increasing the dosage of methadone. Split dosing can also help to correct aberrant metabolism.

3. Medications that Impact on Methadone Metabolism

Various drugs can cause the liver to speed up metabolism. When this occurs most of the methadone is excreted before it can be used. Drugs that cause an increase in metabolism are rifampin for tuberculosis

(Kreek, Gutjahr, Garfield, Bowen and Field, 1976), dilantin for epilepsy (Payte and Khuri, 1992) , carbamazepine (Payte and Khuri, 1992) and more recently St. John's Wort (Shinderman, 2001). Again the best way to correct the problem is to raise the dose and/or break the dose down into several doses throughout a 24 hour period (Payte and Khuri, 1992). For example, a patient on 120 mgs/day might break their dose into thirds taking one third in the morning, one third at dinner time and one third before going to bed. In a sense this helps to maintain the long half life of methadone. Unfortunately, most programs do not utilize this later procedure because of over concern about diversion.

CYP-450 is a liver enzyme and drugs that speed up metabolic rate do so through this enzyme. This is how Tegretol (carbamazepine) and other siezure disorder medications effect methadone, by inducing CYP-450 which them speed up liver metabolism. Tegretol is a strong inducer of hepatic CYP-450 enzyme activity in the liver. The accelerated metabolism may eliminate methadone entirely within 24 hours causing the abstinence syndrome. For most patients raising the dose will work, however in a few cases patients will continue to experience the abstinence syndrome. One procedure to handle this is to rise the dose and split it and finally adding cimetidine (Tagamet) to inhibit liver enzyme activity.

The antibiotic, Nafcillin has the same effect as rifampin (a known methadone villain) and carbamazepine (Taylor, Pritchard, Goldstein and Fletcher, 1994; Wells, Holbrook, Crowther and Hirsh, 1994). So it seems Nafcillin is an inducer of the same CYP-450 enzymes that accelerate metabolism of methadone.

4. Cocaine Use and Opiate Receptors

A recent discovery is that cocaine use can cause an increase in the number of brain opiate receptors (Unterwald, Horne-King and Kreek, 1992). Brain receptors are not static, rather they are chemical bonds floating along the surface of the membrane. The number of receptors for any natural ligand can change dependent of various conditions. As expected an increase in the number of opiate receptors would reduce the action of methadone.

For example, lets say a patient is on 100 mgs/day. Lets use small round numbers to demonstrate this, normally there are hundreds of thousands of opiate receptors in the human brain. For this example when the patient is on a stable dose the number of opiate receptors in the brain averages around 100. And 75 percent of the 100 opiate receptors, or 75 receptors remained filled throughout a 24 hour period. Now this patient begins to use cocaine which causes an increase in the number of opiate receptors to 150. However, only 75 receptors remain filled and active. Now instead of 75 percent of the receptors being filled now only 50 percent are filled. The patient complains that the cocaine is eating up their methadone and asks for a raise. And probably the patient will need their dose to be increased at least 20-30 mgs/day to feel the same.

5. Barbiturates

There has been one or two reports of a barbiturate causing abstinence in a methadone patient. While this is a rare occurrence and the causes have not been determined all methadone patients should be aware of it (Tong et al, 1981).

6. Medications that Impact on Methadone Plasma Concentrations

Some drugs can interact with methadone when it is bound to plasma proteins. As was mentioned above most binding of methadone to plasma proteins is non specific, and this means that many drugs with similar shapes can bind to the same area of the blood protein and knock the methadone molecule out. This can cause a much higher effective blood methadone level, which can be a problem for someone who does not have tolerance or even someone on a low dose of methadone without much of an initial tolerance. Some drugs can knock methadone away from the blood proteins that they are bound to causing a sudden release of methadone to them interact with the opiate receptor. Drugs that can do this are erythromycin, clarithromycin, Vitamin E and many of the NSAIDS (Ibuprofen and Ketoprofen). While the danger is obvious for the individual with a low tolerance these drugs can also have an effect on patients taking a blockade dose with a high tolerance by causing the release of their stored methadone (or buffer) ;and thus destabilizing them. It would probably take a few days to build up the methadone plasma to its initial level.

The antidepressant fluvoxamine (Luvox), used for depression and obsessive compulsive disorder, can reduce the metabolism of methadone significantly, raising blood levels (Bertschy, Baumann, Eap and Buettig, 1994) One asthmatic patient almost died after a doctor prescribed the drug without knowing that the patient was on methadone from elsewhere (Alderman and Frith, 1999). It has also been found that fluoxetine (Prozac) also raises methadone levels, but only of a slight order, perhaps 10% whereas fluvoxamine may do so by 50% or more. It is possible that this effect could

be used 'therapeutically' when higher methadone levels are desired, but it could also be very dangerous.

7. Drugs that Impact on Bioavailability: Vitamin C

Reports have surfaced about patients afraid to take Vitamin C because it would block methadone. Vitamin C does not block methadone but it can change the pH and thus influence the bioavailability. In an acidic environment methadone is not absorbed well and the methadone will be excreted unused. This only occurs at extremely high doses of Vitamin C, like 4 grams a day.

All the vitamin C myth does is to cause fear, apprehension and raise suspicions about methadone. Whoever has promoted this myth is anti-methadone and therefore anti-methadone patient. Why? Because when methadone patients are frightened and suspicious of the very medication that has saved their lives they can not concentrate on the important tasks at hand -- that of changing their lives!

Summary

As more is learned about methadone metabolism the greater clinical knowledge about the many factors can impact on its effectiveness. Unfortunately since many medical professionals are not aware of these recent findings it will be up to patients to insure that they are being prescribed an adequate dose. NAMA will continue to report on new findings and the factors that can interfere with adequate methadone dose.

References

Alderman, C.P. and Frith, P.A. (1999). Fluvoxamine - methadone interaction. **Australia New Zealand Journal of Psychiatry** 33:99-101.

Bertschy, G., Baumann, P., Eap, C.B. and Buettig, D. (1994) Probable metabolic interaction between methadone and fluvoxamine in addict patients. **Therapeutic Drug Monitoring** 16: 42-45.

Cooper, J.R., Bloom, F.E. and Roth, R.H. (1991). **The Biochemical Basis of Neuropharmacology** (6th Edition). New York: Oxford University Press.

Gilman, A.G., Rail, T.W., Niles, A.S. and Taylor, P. (eds) (1990). G**oodman and Gilman's The Pharmacological Basis of Therapeutics** (8th Edition). New York: Pergamon Press.

Kreek, M.J., Garfield, J.W., Gutjahr, C.L. et al (1976). Rifampin-induced methadone withdrawal. **New England Journal of Medicine** 294: 1104-1106.

Leavitt, S.B., Shinderman, M., Maxwell, S., Eap, C.B. and Paris, P. (2000). When "enough" is not enough: New Perspectives on optimum methadone maintenance dose. **Mt. Sinai Journal of Medicine** 67(5&6): 404-411.

Payte, J.T. and Khuri, E. (1992). Principles of methadone dose determination. In: Parrino, M.W. (Chair & Editor). **State Methadone Treatment Guidelines**. Rockville, MD: U.S. Department of Health and Human Services, Center for Substance Abuse Treatment.

Shinderman, M. (2001). Warning: St. John's Wort Reduces Methadone. **NAMA Talk** (February).

Taylor, A.T., Pritchard, D.C., Goldstein, A. O. and Fletcher, J.L. Jr. (1994). Continuation of warfarin-nafcillin interaction during dicolxacillin therapy. **Journal of Family Practice August** 39(2): 182-185.

Tong, T.G., Pond, D.M., Kreek, M.J. et al. (1981). Phenytoin-induced methadone withdrawal. **Annals of Internal Medicine** 94: 349-351.

Unterwald, E.M.; Horne-King, J. and Kreek, M.J. Chronic cocaine alters brain mu opioid receptors. **Brain Research** 1992 584: 314-318.

Wells, P.S., Holbrook, A.M., Crother, N.R. and Hirsh, J. (1994). Interactions of warfarin with drugs and food. **Annals of Internal Medicine** (November 1) 121(9): 676-83.

Education Series
Cost per each $2

Number 1. Methadone Maintenance and Patient Self Advocacy by Arlene Ford. (March, 1991).

Number 2. Drug Policy in the Age of AIDS: The Philosophy of Harm Reduction by Rod Sorge (April, 1991).

Number 3. Myths About Methadone by Emmett Velten (March, 1992).

Number 4. Methadone, HIV Infection and Immune Function by Herman Joseph (August, 1994).

Number 5.1. The Basics of Pharmacology, Basic Pharmacology: How Methadone Works? by J.T. Payte, Jeffrey Smith and Joycelyn Woods (February, 2001 Revised).

Number 5.2. The Pharmacology of Opioids, Basic Pharmacology: How Methadone Works? by J.T. Payte, Jeffrey Smith and Joycelyn Woods (February, 2001 Revised).

Number 5.3. Drugs and Conditions That Impact On the Action of Methadone, Basic Pharmacology: How Methadone Works? by J.T. Payte, Jeffrey Smith and Joycelyn Woods (February, 2001 Revised).

Number 6. Starting A Patient Run Program (Not available in revision).

Number 7. Managed Care, Medicaid, Medicare and Private Insurance: Who Will Pay? (Not available in revision).

Number 8. Methadone Does Not Work Bibliography (October, 1995).

Number 9. The Methadone Maintained Patient and the Treatment of Pain by J. Thomas Payte, Elizabeth Khuri, Herman Joseph and Joycelyn Woods (January, 1999).

Membership in NAMA is $25 a year for Individual and $40 for International Membership. Additional family members may join at the cost of $10 each a year. Institutional Membership is $110 a year for U.S. and International. If you cannot afford membership dues, or can only afford a part of it, NAMA will still accept your membership request.

NAMA Manuals
Cost per each $10

Number 1 Starting a Methadone Advocacy Group (NAMA Chapter or Affiliate). The basics of starting a methadone advocacy group including history of methadone advocacy, forming a Board of Directors, meeting planning, first projects, politics of methadone, listing of state agencies and other resources.

Setting Up a 12 Step Group. A manual to help patients and professionals start a 12 step group. Includes organizing the group, meeting planning, the basics of starting a 12 step group, a generic version of 12 steps and other resources.

The price of the Education Series and Manuals are to cover the cost of duplicating and mailing.

NAMA is a not-for-profit organization.

For membership please complete & mail the coupon below with your dues.

Coupon

Name: _____

Organization: _____

_____

Address: _____

_____

City: _____ **State**: _____

Country: _____ **Postalcode**:_____

Work Phone: _____

Home Phone: _____

Fax: _____

Amount Enclosed: _____