FDA Drug Safety Communication: Serious CNS reactions possible when methylene blue is given to patients taking certain psychiatric medications

Safety Announcement

Additional Information for Patients

Additional Information for Healthcare Professionals

Data Summary

References

Safety Announcement

[07-26-2011] The U.S. Food and Drug Administration (FDA) has received reports of serious central nervous system (CNS) reactions when the drug methylene blue is given to patients taking psychiatric medications that work through the serotonin system of the brain (serotonergic psychiatric medications). Methylene blue is commonly used in diagnostic procedures and is also used to treat a number of medical conditions (see Facts about methylene blue box). A list of the serotonergic psychiatric medications that can interact with methylene blue can be found here.

Although the exact mechanism of this drug interaction is unknown, methylene blue inhibits the action of monoamine oxidase A—an enzyme responsible for breaking down serotonin in the brain. It is believed that when methylene blue is given to patients taking serotonergic psychiatric medications, high levels of serotonin can build up in the brain, causing toxicity. This is referred to as Serotonin Syndrome. Signs and symptoms of Serotonin Syndrome include mental changes (confusion, hyperactivity, memory problems), muscle twitching, excessive sweating, shivering or shaking, diarrhea, trouble with coordination, and/or fever.

Healthcare professionals and patients may not realize that methylene blue has monoamine oxidase inhibitor (MAOI) properties. Methylene blue should generally not be given to patients taking serotonergic drugs. However, there are some conditions that may be life-threatening or require urgent treatment with methylene blue such as when it is used in the emergency treatment of:

- methemoglobinemia,
- ifosfamide-induced encephalopathy, or
- cyanide poisoning.

Safety information about these potential drug interactions and important drug usage recommendations for emergency and non-emergency situations are being added to the drug labels for serotonergic psychiatric medications. (See Additional Information for Healthcare Professionals)

A separate Drug Safety Communication (DSC) is being released today for linezolid (Zyvox) due to similar potential drug interactions with serotonergic psychiatric medications and includes drug usage recommendations.

Health Canada issued a NOTICE TO HOSPITALS on the association of serotonin toxicity with methylene blue in combination with serotonin reuptake inhibitors on February 16, 2011.

Facts about Methylene Blue

- Used to treat methemoglobinemia, vasoplegic syndrome, ifosfamide-induced encephalopathy, cyanide poisoning
- Used as a dye in therapeutic and diagnostic applications
- Is a potent, reversible monoamine oxidase inhibitor (MAOI).
Additional Information for Patients

- You may need to temporarily stop taking your serotonergic psychiatric medication if it becomes necessary for you to take methylene blue in certain situations. Your healthcare provider will tell you when to start methylene blue after stopping your serotonergic psychiatric medication.
- **Do not** stop taking your serotonergic psychiatric medicine without first talking to a healthcare professional.
- Make sure your healthcare professional knows about all the medications you are taking. It is helpful to keep a list of all your current medications in your wallet or another location where it is easily retrieved.
- Contact your healthcare professional immediately if you are taking a serotonergic psychiatric medication and develop any of the following symptoms: mental changes (confusion, hyperactivity, memory problems), muscle twitching, excessive sweating, shivering or shaking, diarrhea, trouble with coordination, and/or fever.
- Discuss any questions or concerns about methylene blue or serotonergic psychiatric medications with your healthcare professional.
- Report any serious side effects you experience to the FDA MedWatch program using the information in the "Contact Us" box at the bottom of the page.

Additional Information for Healthcare Professionals

- Methylene blue can interact with serotonergic psychiatric medications and cause serious CNS toxicity.
- **In emergency situations** requiring life-threatening or urgent treatment with methylene blue (as described above), the availability of alternative interventions should be considered and the benefit of methylene blue treatment should be weighed against the risk of serotonin toxicity. If methylene blue must be administered to a patient receiving a serotonergic drug, the serotonergic drug must be immediately stopped, and the patient should be closely monitored for emergent symptoms of CNS toxicity for two weeks (five weeks if fluoxetine [Prozac] was taken), or until 24 hours after the last dose of methylene blue, whichever comes first.
- **In non-emergency situations** when non-urgent treatment with methylene blue is contemplated and planned, the serotonergic psychiatric medication should be stopped to allow its activity in the brain to dissipate. Most serotonergic psychiatric drugs should be stopped at least 2 weeks in advance of methylene blue treatment. Fluoxetine (Prozac), which has a longer half-life compared to similar drugs, should be stopped at least 5 weeks in advance.
  - Treatment with the serotonergic psychiatric medication may be resumed 24 hours after the last dose of methylene blue.
  - Serotonergic psychiatric medications should not be started in a patient receiving methylene blue. Wait until 24 hours after the last dose of methylene blue before starting the antidepressant.
  - Educate your patients to recognize the symptoms of serotonin toxicity or CNS toxicity and advise them to contact a healthcare professional immediately if they experience any symptoms while taking serotonergic psychiatric medications or methylene blue.
  - Report adverse events involving methylene blue or serotonergic psychiatric medications to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.

Data Summary

FDA has received adverse event reports from the FDA Adverse Event Reporting System (AERS) database of serious central nervous system (CNS) reactions in patients treated with serotonergic psychiatric medications who were administered methylene blue. Additional cases also have been reported in the published literature.\(^1\)\(^-\)\(^3\) The reported adverse events include the following: lethargy, confusion, delirium, agitation, aggression, obtundation, and coma. These symptoms were frequently accompanied by neurological symptoms, such as myoclonus, expressive aphasia, hypertonia, and seizures, or autonomic symptoms, such as pyrexia and elevated blood pressure.

Based on the available information provided in the AERS cases and literature, FDA has concluded that the concomitant administration of a serotonergic psychiatric medication with methylene blue has the potential for a drug interaction causing serotonin syndrome. It appears this potential drug interaction can also occur following the discontinuation of serotonergic psychiatric medications with long half-lives. As a result, methylene blue should generally not be given to patients taking serotonergic drugs unless the benefit is deemed to outweigh the risk.

References

**Tables - Psychiatric medications with serotonergic activity**

**Selective Serotonin Reuptake Inhibitors (SSRIs)**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Found in Brand name(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>paroxetine</td>
<td>Paxil, Paxil CR, Pexeva</td>
</tr>
<tr>
<td>fluvoxamine</td>
<td>Luvox, Luvox CR</td>
</tr>
<tr>
<td>fluoxetine</td>
<td>Prozac, Sarafem, Symbyax</td>
</tr>
<tr>
<td>sertraline</td>
<td>Zoloft</td>
</tr>
<tr>
<td>citalopram</td>
<td>Celexa</td>
</tr>
<tr>
<td>escitalopram</td>
<td>Lexapro</td>
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</table>

**Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Found in Brand name(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>venlafaxine</td>
<td>Effexor, Effexor XR</td>
</tr>
<tr>
<td>desvenlafaxine</td>
<td>Pristiq</td>
</tr>
<tr>
<td>duloxetine</td>
<td>Cymbalta</td>
</tr>
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</table>

**Tricyclic Antidepressants (TCAs)**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Found in Brand name(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>amitriptyline</td>
<td>Amitid, Amitril, Elavil, Endep, Etrafon, Limbitrol, Triavil</td>
</tr>
<tr>
<td>desipramine</td>
<td>Norpramin, Pertofrane</td>
</tr>
<tr>
<td>clomipramine</td>
<td>Anafranil</td>
</tr>
<tr>
<td>imipramine</td>
<td>Tofranil, Tofranil PM, Janimine, Pramine, Presamine</td>
</tr>
<tr>
<td>nortriptyline</td>
<td>Pamelo, Aventyl hydrochloride</td>
</tr>
<tr>
<td>protriptyline</td>
<td>Vivactil</td>
</tr>
<tr>
<td>doxepin</td>
<td>Sinequan, Zonalon, Silenor</td>
</tr>
<tr>
<td>trimipramine</td>
<td>Surmontil</td>
</tr>
</tbody>
</table>

**Monoamine Oxidase Inhibitors (MAOIs)**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Found in Brand name(s)</th>
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</thead>
<tbody>
<tr>
<td>Isocarboxazid</td>
<td>Marplan</td>
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<tr>
<td>Phenelzine</td>
<td>Nardil</td>
</tr>
<tr>
<td>Selegiline</td>
<td>Emsam, Eldepryl, Zelapar</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>Parnate</td>
</tr>
</tbody>
</table>

**Other Psychiatric Medications**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Found in Brand name(s)</th>
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</thead>
<tbody>
<tr>
<td>amoxapine</td>
<td>Asendin</td>
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<tr>
<td>maprotiline</td>
<td>Ludiomil</td>
</tr>
<tr>
<td>nefazodone</td>
<td>Serzone</td>
</tr>
</tbody>
</table>
Related Information

- **Methylene blue injectable in combination with serotonin reuptake inhibitors - Association with serotonin toxicity** - Notice to Hospitals

  Health Canada

- **FDA Drug Safety Communication: Serious CNS reactions possible when linezolid (Zyvox) is given to patients taking certain psychiatric medications**

  7/26/2011

- **FDA Drug Safety Podcast for Healthcare Professionals: Serious CNS reactions possible when methylene blue is given to patients taking certain psychiatric medications**

  8/1/2011

- **Comunicado de la FDA sobre la seguridad de los medicamentos: Posibles reacciones graves en el SNC cuando se administra azul de metileno a pacientes que toman ciertos medicamentos psiquiátricos.**

Contact Us

- **Report a Serious Problem**

- 1-800-332-1088

- 1-800-FDA-0178 Fax

  MedWatch Online

  Regular Mail: Use postage-paid FDA Form 3500

  Mail to: MedWatch 5600 Fishers Lane

  Rockville, MD 20857

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5. /Drugs/DrugSafety/ucm265305.htm


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