BRIGHAM AND WOMEN'S HOSPITAL

DESCRIPTION OF THE IMPLEMENTATION OF A CLINICAL DECISION SUPPORT ALERT IN RESPONSE TO A CASE REPORT OF A PREVENTABLE ADVERSE DRUG EVENT

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Information Systems

Partners HeatlhCare System

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Objective

- Clinical Decision Support Systems
- Case Report of Medication Error
- Editor of Newsletter
- Attended Board of Pharmacy meeting
- Case of death due to sepsis
- Patient prescribed known interacting drugs
- Utilize this information to create an alert

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Introduction

- Clinical Decision Support Systems (CDSS)
- Azathioprine/6-mercaptorpurine (the metabolic product of azathioprine)
- Listed in Micromedex® as both a DDI and therapeutic duplication
- How do we integrate this piece of knowledge into CDSS
- Medical Knowledge Committee (MKC)

6-Mercaptopurine/Azathioprine DDI

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MERCAPTOPURINE

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  - Drug Properties
  - Storage and Stability
  - Adult Dosage
  - Pediatric Dosage
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  - Onset and Duration
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  - ADME
- Cautions
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3.5.1.C Azathioprine

1) Interaction Effect: myelosuppression, impaired renal function, and hepatotoxicity
2) Summary: Mercaptopurine is an active metabolite of azathioprine (Prod Info IMURAN(R) oral tablets, IV injection, 2005). Profound myelosuppression, severe sepsis and subsequent death has been reported in a patient who took azathioprine 150 mg once a day with mercaptopurine 100 mg daily (None Listed, 2006). It is clinically unnecessary and inadvisable to use these two medications simultaneously.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Mercaptopurine is an active metabolite of azathioprine. Concomitant administration should be avoided.
7) Probable Mechanism: additive adverse effects

3.5.1.D Bacillus of Calmette and Guerin Vaccine, Live

1) Interaction Effect: an increased risk of infection by the live vaccine
2) Summary: Vaccination with a live vaccine in a patient immunocompromised by a chemotherapeutic agent has resulted in severe and fatal infections (MMWR, 1989; Rosenbaum et al, 1966). One patient experienced disseminated vaccinia infection after receiving a smallpox vaccine while on concomitant methotrexate therapy (Allison, 1968). Live virus and bacterial vaccines should not be administered to a patient receiving an immunosuppressive chemotherapeutic agent. At least three months should elapse between the discontinuation of chemotherapy and vaccination with a live vaccine (MMWR, 1989).
3) Severity: major
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Patients receiving immunosuppressive chemotherapy should not be vaccinated with a live vaccine. In patients with leukemia in remission, allow at least three months between the end of chemotherapy and vaccination with a live vaccine.
7) Probable Mechanism: decreased immune response allows live vaccine to produce infection

3.5.1.E Balsalazide

1) Interaction Effect: an increased risk of myelosuppression
2) Summary: 6-mercaptopurine is metabolized by thiopurine methyltransferase (TPMT), an enzyme which converts the drug to 6-methylmercaptopurine. Decreased TPMT activity causes increased active metabolites of 6-mercaptopurine to accumulate, which has been associated with an increased risk of life-threatening myelosuppression. Balsalazide is a relatively potent inhibitor of TPMT activity. Therefore, careful monitoring of blood counts is recommended in patients receiving concomitant therapy with 6-mercaptopurine and balsalazide (Lowry et al, 1999).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Caution should be exercised when coprescribing balsalazide and 6-mercaptopurine. Complete blood counts should be closely monitored.
7) Probable Mechanism: inhibition by balsalazide of thiopurine methyltransferase

3.5.1.F Measles Virus Vaccine, Live

1) Interaction Effect: an increased risk of infection by the live vaccine
2) Summary: Vaccination with a live vaccine in a patient immunocompromised by a chemotherapeutic agent has resulted in severe and fatal infections (MMWR, 1989; Rosenbaum et al, 1966). One patient experienced disseminated vaccinia infection after receiving a smallpox vaccine while on concomitant methotrexate therapy (Allison, 1968). Live virus and bacterial vaccines should not be administered to a patient receiving an immunosuppressive chemotherapeutic agent. At least three months should elapse between the discontinuation of chemotherapy and vaccination with a live vaccine (MMWR, 1989).
3) Severity: major
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Patients receiving immunosuppressive chemotherapy should not be vaccinated with a live vaccine. In patients with leukemia in remission, allow at least three months between the end of chemotherapy and vaccination with a live vaccine.
7) Probable Mechanism: decreased immune response allows live vaccine to produce infection

3.5.1.G Mesalamine

1) Interaction Effect: an increased risk of myelosuppression
2) Summary: Six-mercaptopurine is metabolized by thiopurine methyltransferase (TPMT), an enzyme which converts the drug to 6-methylmercaptopurine. Decreased TPMT activity causes the accumulation of active metabolites of 6-mercaptopurine, which has been associated with an increased risk of life-threatening myelosuppression. Mesalamine is a relatively potent inhibitor of TPMT activity. Therefore, careful monitoring of blood counts is recommended in patients receiving concomitant therapy with 6-mercaptopurine and mesalamine (Prod Info Purinethol(R), 2002b).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Caution should be exercised with the coadministration of mesalamine and mercaptopurine. Complete blood counts should be closely monitored

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Therapeutic Duplication

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3.1 Contraindications

A) hypersensitivity to mercaptopurine/component of formulation
B) prior resistance to mercaptopurine or thioguanine
C) should not be used unless acute leukemia diagnosis is established

3.2 Precautions

A) do not administer concomitantly with azathioprine; therapeutic duplication as azathioprine is metabolized to mercaptopurine (None Listed, 2006; Prod Info IMURAN(R) oral tablets, IV injection, 2005)
B) individuals with inherited deficiency of enzyme thiopurine methyltransferase (TMPT) (Prod Info mercaptopurine oral tablets, 2003)
C) liver disease; increased risk of hepatic toxicity (Prod Info mercaptopurine oral tablets, 2003)
D) use proper procedures for handling and disposal of chemotherapy

3.3 Adverse Reactions

Dermatologic Effects
Endocrine/Metabolic Effects
Gastrointestinal Effects
Hematologic Effects
Hepatic Effects
Immunologic Effects
Musculoskeletal Effects
Renal Effects
Reproductive Effects
Respiratory Effects
Other

3.3.2 Dermatologic Effects

Dermatological finding
Hand-foot syndrome due to cytotoxic therapy

3.3.2.A Dermatological finding

1) An erythematous RASH, with or without a papular and/or scaly component, occurred in 8 patients (16 episodes) within 3 weeks of stopping mercaptopurine or mercaptopurine and methotrexate (Kirk et al, 1987). It sometimes had an acneiform appearance. The DERMATITIS was pruritic and primarily developed around the mouth, but also occurred on the upper chest and the dorsal aspects of the forearms and hands. The rash did not respond to sun avoidance, topical steroids, topical clindamycin, or emollients, but cleared spontaneously in 2 to 8 weeks. Similar types of transient skin rashes were observed in 48% of leukemic children 1 to 12 weeks (mean 4.5 weeks) after completing maintenance therapy with methotrexate and mercaptopurine (Shaw & Eden, 1989).
2) HYPERPIGMENTATION may be associated with mercaptopurine therapy (Prod Info Purinethol(R), 1999).

3.3.2.B Hand-foot syndrome due to cytotoxic therapy

1) Palmar-plantar erythema with desquamation of the fingers occurred in a 32-year-old male receiving mercaptopurine 400 milligrams/day and allopurinol 200 milligrams/day for less than 2 weeks. Mercaptopurine was discontinued and topical FLUOCINONIDE ointment under occlusion was applied. The erythema and pain resolved within 96 hours (Cox & Robertson, 1986a).

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Hyperuricemia

1) Hyperuricemia may develop in patients as a result of extensive purine catabolism and rapid cell lysis. This adverse effect may be minimized by increasing hydration, urine alkalinization and allopurinol prophylaxis. Reduce the dosage of mercaptopurine by one- quarter to one-third when giving concurrently with allopurinol (Prod Info Purinethol(R), 1999).

3.3.4 Gastrointestinal Effects

Gastrointestinal tract finding
Pancreatitis

3.3.4.A Gastrointestinal tract finding

1) NAUSEA, VOMITING, ANOREXIA, and oral lesions resembling thrush have occasionally been reported with mercaptopurine therapy (Prod Info Purinethol(R), 1999).

3.3.4.B Pancreatitis

1) Isolated cases of pancreatitis have been reported in patients taking 50 to 125 milligrams daily of mercaptopurine for Crohn's disease or ulcerative colitis. The onset is

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Methods

- Present information to MKC
- MKC's Medical Director is concerned that others will try to utilize exception to propose therapeutic duplications as inclusion in DDI knowledge base
- Utilization of TD will allow only outpatient clinicians to see alert
- Inpatient pharmacists are the ONLY one alerted in CPOE

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Pharmacy OE/Pre-Implementation

INPATIENT PHARMACY (ASpk) - Microsoft Internet Explorer provided by Partners HealthCare System

Address http://ppd.partners.org/scripts/phsweb.mwl?APP=RX&OPT=rx&oerec=1871359%20112628377&rxrec=&rxflag=Pend&patid=16356792&session=1

163-56-79-2 OETEST,WILHEMINA | DOB: 05/01/30 | Age: 76 | Gender: F | Weight: 66.6kg

Order Entry: AZATHIOPRINE 150 MG PO DAILY

Allergies: Dairy Products-->Anaphylaxis,; Sulfa-->test; Shellfish-->Hypotens...

Rm: 17A-501

Medication | Total dose: | TY | Cost

AZATHIOPRINE TABLET | 1.9

NEW ENTRY

Therapeutic Message -- Web Page Dialog

Please review medication profile for mercaptopurine orders.

The administration of mercaptopurine and azathioprine to a patient is CONTRAINDICATED. Mercaptopurine is a metabolite of azathioprine. When taken together, these medications have profound adverse effects.

OK

Freq QD | day | dose | hour

Start 09/21/06 15:00 | Send Dose Now

End 09/28/06 08:00 | Adm Times

PRN | FTC | Days

NOT SM | N/A ON SM | Cart: 2 | Type2 | Instr

Approve | AcK | RxHold | ViewLink | Cancel

Labs | DieT | DRuGLab | Feedback | Profile | PreV | Next | PendQ | Zoom | CPC | PHB

Opening page http://ppd.partners.org/scripts/phsweb.mwl?APP=RX&OPT=rx&oerec=1871359 1

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Results

- After discussion with Medical Director of MKC, present information to full MKC
- The concerns of Medical Director of MKC also presented at meeting
- These are taken into account in conjunction with presented material
- Decision is made to include in DDIs as benefits outweigh risk

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Screen Shot CPOE Inpatient/Post Implementation

BICS Terminal Emulator - OMABICS14.partners.org

ViewOrders PtLookup Feedback Help Goodbye

OETEST,WILHEMINA 76F 16356792 Adm: 11/01/91 Room: 17A-501

DRUG WARNING(S) FOUND

Current Order: OETEST,WILHEMINA

6-MERCAPTO-PURINE PO

Warnings:

SERIOUS INTERACTION (AZATHIOPRINE SODIUM)

Display info

Message:

PT. IS ON AZATHIOPRINE AND MERCAPTOPURINE-MERCAPTOPURINE IS A METABOLITE OF AZATHIOPRINE AND CONC USE RISKS MYELOSUPRESSION/SEPSIS-REC TO AVOID CONC US

(*)C Cancel order
( )K Keep (override) order

Ok

Use up & down arrow keys to read warning messages.

QuickTime Player
ismpmsa11-...
Roxio DigitalMe...
ISMPNurseN...
Start CinePlayer
IMP DOcs
Preventable ADEs by ...
2218.pdf
6mpAzathio...
Amendment to MIMEPS par...
~$pAzathio...
Click'N Design 3D

Start | Inbox - Micr... | Study Data... | ePrescribin... | Patient_Hdr | CareGroup ... | My Comput... | Leo McKenn... | LMR OMA4... | BICS Term... | 6mpAzathio... | 3:55 PM

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Screen Shot Outpatient/Post Implementation

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Address http://lmrintra.partners.org/scripts/phsweb.mwl?APP=LMR&SESSION=70526936

Oetest,Bridget May PG AS824

11489986 (BWH) 02/13/1934 (72 yrs.) F SJP

Select | Desktop | Pt Chart: Medications | Oncology | Custom | Reports | Admin | Sign | Results | ? | Resource | Popup

Warning

You are ordering: 6-MP (MERCAPTOPURINE)

Drug - Drug Interaction

Alert Message	Keep New Order - select reason(s)
Patient is currently on: **AZATHIOPRINE 75MG PO QD** Patient is on Azathioprine and Mercaptopurine - Mercaptopurine is a metabolite of Azathioprine and as such, should not be administered concurrently due to risk of myelosupression and sespsis - Rec. to avoid concurrent use.	○ Will D/C pre-existing drug **Reasons for override:** ☐ Will adjust dose as recommended ☐ Will monitor as recommended ☐ Patient has already tolerated combination ☐ No reasonable alternatives ☐ Other

Continue New Order | Cancel | Back To Lookup

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Conclusion

- Utilization of medication error data can enhance CDSS
- Information must be presented in a logical, concise form
- Utilization of team concept ensures all issues are vetted and contributes to a more robust knowledge structure

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