

**ADR Focus**

**Preventing Fatalities Associated with Intravenous Colchicine Therapy**

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*Editor's Note: Adverse drug reactions experienced by UWMC or HMC patients and reported to the pharmacy are reviewed quarterly by the Pharmacy & Therapeutics Committee. Following the Committee's review, a summary is published in this newsletter (see page 60) along with a companion article regarding some aspect of adverse drug reactions. It is hoped that these articles will be useful tools to remind prescribers of the fundamental principle of pharmacology that states, "No drug has only one action." By reminding prescribers to be alert to the appearance of undesired and unintended actions of drugs, therapeutic outcomes may be improved and adverse events minimized. If you have a patient you feel is experiencing an Adverse Drug Reaction, report it by calling the A.D.R. Phone Line, HMC: 731-3802; UWMC: 598-6837; SCCA: 288-6336.*

Colchicine is frequently used because of its anti-inflammatory properties to treat both acute attacks of gout and to prevent recurrent attacks. The drug is sometimes administered intravenously to treat acute gouty arthritis when other medications are not effective, when the patient is unable to take medications orally, or when rapid therapeutic intervention is necessary.<sup>1</sup> Inappropriate intravenous (IV) colchicine administration has been associated in the medical literature with preventable fatalities.<sup>2</sup> The purpose of this ADR Focus is to explore the issue of inappropriate IV colchicine administration and to provide practitioners with guidelines for its safe use.

Specific guidelines have been established for the safe and appropriate administration of IV colchicine (see Table I). Invariably, reported fatalities associated with colchicine administration via this route occurred when guidelines were not followed or when guidelines were interpreted incorrectly by the health care practitioner. The problem is compounded by the fact that intravenously administered colchicine lacks early gastrointestinal warning symptoms that can be a harbinger of serious systemic toxicity.<sup>2</sup>

Bonnell et al. identified and analyzed 20 deaths that occurred between 1983 and 2000 that were attributed to inappropriate IV colchicine administration.<sup>2</sup> These cases were taken from the medical literature and from FDA's Adverse Event Reports System (AERS). Seventeen of the patients received colchicine for the treatment of gout, two for familial Mediterranean fever, and one for an unknown indication. In all 20 cases, the recommended maximum cumulative colchicine dose during a single course of therapy (2-4mg) was exceeded. The total cumulative doses in the analyzed cases ranged from 5.5mg to 19mg.

All treated patients developed various symptoms associated with systemic colchicine toxicity, including: thrombocytopenia, pancytopenia, leukopenia, agranulocytosis,

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A University of Washington / Harborview Medical Center Drug Information Center publication  
Distributed monthly by authority of the Pharmacy and Therapeutics Committee  
Editor: Nelda A. Murri, Pharm.D. (206) 598-6612 – Asst. Editor: Elizabeth Rudy, D.V.M., R.Ph.  
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**UWMC/HMC ADVERSE DRUG REACTION SUMMARY**  
**Fiscal Year 2002/2003**  
**1st Quarter (July 2002-September 2002)**

**University of Washington Medical Center**

- ◆ A total of 46 adverse drug reactions were reported at UWMC this quarter.
- ◆ These ADRs were reported by physicians, nurses, and pharmacists.
- ◆ Thirty-three inpatients and thirteen outpatients experienced an ADR this quarter.
- ◆ The drug class for which the largest numbers of ADR reports were filed was antibiotics- 10.
- ◆ The ADR reaction types<sup>†</sup> reported were: augmented- 15, hypersensitivity- 15, idiosyncratic- 15, and unknown- 1.
- ◆ Adverse drug reaction severity ratings<sup>‡</sup> included: unknown- 1, mild- 26, moderate- 17, and severe- 2.
- ◆ According to the Naranjo Algorithm, the likelihood that the administered drug was responsible for the reported ADR was “unknown” in 3 reports, “probable” in 26 reports, “possible” in 15 reports, and “highly probable” in 2 reports.
- ◆ Six ADR reports were submitted to the FDA this quarter.

**Harborview Medical Center**

- ◆ A total of 58 adverse drug reactions were reported at HMC this quarter.
- ◆ These ADRs were reported by pharmacists, nurses, physicians, and CT technicians.
- ◆ Forty-eight inpatients and ten outpatients experienced an ADR this quarter.
- ◆ The drug class for which the largest numbers of ADR reports were filed was antibiotics- 18.
- ◆ The ADR reaction types<sup>†</sup> reported were: augmented- 30, hypersensitivity- 17, and idiosyncratic- 11.
- ◆ Adverse drug reaction severity ratings<sup>‡</sup> included: mild- 40, moderate- 11, and severe- 7.
- ◆ According to the Naranjo Algorithm, the likelihood that the administered drug was responsible for the reported ADR was “definite” in 2 reports, “probable” in 31 reports, and “possible” in 25 reports.
- ◆ Seven ADR reports were submitted to the FDA this quarter.

<sup>†</sup> ADR reaction type definitions- **Augmented**: reactions consistent with the pharmacology of the drug; **Idiosyncratic**: unusual reaction independent of the pharmacology of the drug; **Hypersensitivity**: newly identified allergy or one previously identified; **False Alarm**: reaction deemed not related to drug therapy.

<sup>‡</sup> ADR reaction severity rating definitions- **Insignificant**: requires no change in therapy; **Mild**: requires therapeutic intervention but no change in length of hospital stay; **Moderate**: requires intervention and increased length of hospital stay by at least one day; **Severe**: life threatening, contributes to death or permanent disability, or recovery takes greater than 2 weeks.

**Preventing Fatalities Associated with IV Colchicine Therapy** (continued)

**Symptoms of Colchicine Toxicity<sup>7</sup>**

Abdominal pain  
 Arthralgia  
 Ascending paralysis  
 Bone marrow depression  
 Cyanosis  
 Delirium  
 Diarrhea  
 Dilated pupils  
 Difficulty swallowing  
 Hematuria  
 Myalgia  
 Nausea  
 Oliguria  
 Seizures  
 Sensation of suffocation  
 Shock  
 Tightness in chest  
 Vomiting

aplastic anemia, disseminated intravascular coagulation, and acute renal failure. Sixteen (80%) of the patients developed bone marrow depression that was clinically significant. Death occurred within 1–40 days after administration of the drug. Additionally, 13 of the patients were identified as having other risk factors that could have contributed to an increased risk for serious toxicity from an excessive IV dose of colchicine. These risk factors included: age >65 years, cardiac disease, diabetes, hypertension, renal impairment, concurrent NSAID use, and history of recent oral colchicine therapy.

In their review, Bonnel et al. concluded that the majority of fatalities and adverse events reported following IV colchicine administration could be attributed to medication errors at the time of prescribing or misinterpretation of prescribing guidelines. Additionally, they theorized that in most cases, it didn't appear that colchicine toxicity was acutely identified or specifically treated. Two other retrospective studies support the findings of Bonnel, et al. One reviewed a teaching hospital's four-year experience with the administration of IV colchicine and discovered a 2% incidence of death due to inappropriate administration of the drug.<sup>3</sup> The other reviewed the hospital records for patients at two institutions who received IV colchicine during an 18-month period and found that errors in prescribing occurred in 5 of 19 patients (26%).<sup>4</sup>

Based on the above reports, it appears that reminding practitioners about the safe and appropriate administration of IV colchicine would be a simple but vital first step towards preventing deaths associated with IV administration of this drug. Strategies recom-

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**Recommended strategies for reminding practitioners about the safe and appropriate administration of IV colchicine: a simple but vital first step toward preventing deaths and improving patient safety.**

**There is no clear separation of nontoxic, toxic and lethal doses of colchicine. Fatalities have occurred after IV administration of cumulative doses of only 5 mg.**

**IV administration of colchicine is not recommended in severe hepatic function impairment because of the high risk of impaired elimination and resultant toxicity.**

**IV colchicine administration may exacerbate pre-existing leukopenia.**

mended to achieve this goal include:

- Familiarize prescribers with the recommended guidelines for IV colchicine administration (see Table I);
- Establish institution-specific protocols to help insure patient safety;
- Familiarize providers with the symptoms of colchicine toxicity so that so that the drug can be discontinued and symptoms promptly treated, possibly reducing the likelihood of death (see sidebar on page 60);<sup>2</sup>
- Educate providers regarding the importance of prescribing IV colchicine based on knowledge of a patient's history of oral colchicine use, their renal and hepatic function, and their age;<sup>2</sup> and
- Discourage IV colchicine administration when better treatment alternatives exist.<sup>3</sup>

**Table I: Guidelines for the Use of IV Colchicine for Relief of Acute Gout Attack<sup>3-6</sup>**

1. Single IV dose should not exceed 2mg and cumulative total dose via any route should not exceeding 4mg.
2. After the prescribing limit has been reached, no more colchicine should be administered by any route for at least 7 days.
3. Limit IV therapy to a maximum of 1-2mg in patients who have recently received oral colchicine.
4. Doses must be reduced in the presence of renal disease.
  - a) Patients receiving hemodialysis should not receive colchicine.
  - b) Creatinine clearance 10-50 mL/minute: dose should be decreased by 50% (Cumulative total dose not to exceed 2 mg).
  - c) For all geriatric patients, the cumulative total dose should not exceed 2mg. After the prescribing limit has been reached, additional colchicine should not be administered by any route for at least 21 days.
5. IV and oral doses should not be substituted milligram-for-milligram; IV doses should be no greater than one-half the oral dose.
6. Contraindications (also see sidebar opposite):
  - a) Concurrent renal and hepatic disease.
  - b) Creatinine clearance <10 mL/minute (including patients receiving hemodialysis).
  - c) Extrahepatic biliary obstruction.

## References

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7. Cain H. Flint's emergency treatment and management. Philadelphia: W.B.Saunders; 1980.

## Pharmacy & Therapeutics Committee Actions

Formulary Addition	Dosage Form(s), Strength(s), & Cost <sup>‡</sup>	Therapeutic Classification	Use	Usual Adult Starting Dose*
Ziprasidone (Geodon)	Injection: 20 mg/mL-\$29.12	Atypical antipsychotic	Acutely agitated patients with schizophrenia	Refer to product labeling
	Note: Added to formulary restricted to use by Psychiatry service.			
Formulary Deletion	Dosage Form(s), Strength(s)	Therapeutic Classification	Use	Comment
Metformin XR (Glucophage XR)	All dosage forms and strengths	Biguanide	Type 2 Diabetes	Replaced by non-sustained release formulation
Other Formulary Actions				
Therapeutic Substitution	Product		UWMC Formulary Substitution	
	beclomethasone (Beconase/Vancenase) aerosol nasal inhaler 1-2 sprays (42-84mcg) each nostril 2-4times/day		budesonide (Rhinocort) aerosol nasal inhaler 2 sprays (64mcg) each nostril BID	

\* Refer to product labeling for full prescribing information. ‡ Costs represent UWMC/HMC outpatient acquisition costs and do not include pharmacy dispensing fees.

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3. Locate the yellow "New" icon labeled: ADD THE UWMC/HMC DRUG FORMULARY TO YOUR PDA! and follow the instructions.

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**VOL. 31, NO. 12**

**Supplement:  
Contemporary Issues  
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