VANCOUVER HOSPITAL & Health Sciences Centre

DRUG AND THERAPEUTICS NEWSLETTER

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INDEX

UPDATED POLICY AND PROCEDURES

1. Revised Drug Administration Policies

Dimenhydrinate may be administered **subcutaneously in all areas of the hospital**.

2. Parenteral Drug Therapy Manual (PDTM)

All PDTMs at VHHSC have been inserted with a new December 1995 update. If there are any questions concerning this manual, please contact Mr. Kenn Koo 875-4077 or Mr. Paul Yu 822-7249.

3. Automatic Stop Order Policy

The automatic stop order policy has been revised to the following: "A physician may indicate a specific time limit on any order which will override the automatic stop date. A definite number of doses or time must be specified and may not exceed one year. 'Duration of hospital stay' is not considered acceptable."

RESEARCH AWARDS

We are pleased to announce that the Department of Pharmacy has won two Canadian Society of Hospital Pharmacists national competitive research awards this year. The winning project titles were "Antibiotic Therapeutic Interchange Program (TIP): Six years of experience**"** (Luciana Frighetto, Donna Nickoloff and Peter Jewesson) and "Computer-Assisted Retrospective Clinical Activities Statistics (CARCAS): Three years of experience" (Eric Lun, Luciana Frighetto, Cathy MacDougall and Peter Jewesson).

QUESTION

What is the role of methadone in chronic cancer pain?

Morphine is the mainstay of pain control in cancer patients. Its short half-life allows rapid dose titration in patients with fluctuating degrees of pain and progressive disease.[1] However, some patients may demonstrate inadequate analgesia despite escalating doses of morphine, intolerable side effects, or a true morphine allergy. There are increasing reports of the effectiveness of methadone, a long-acting synthetic opioid analgesic, in controlling terminal cancer pain where high doses of morphine have been ineffective.[2-5]

Table 1 compares the pharmacokinetics of oral methadone and morphine.[1,6] Of note, methadone is only available orally in Canada.

Table 1. Pharmacokinetic comparison of oral methadone and morphine[1,6]

Drug	Methadone	Morphine
Bioavailability (%)	84±26	38±17
Elimination Half-Life (hrs)	30±7.7	3.4±1.9
Time to Peak Analgesia	1-2 hrs	1-2 hrs
Duration of Analgesia (hrs) Single Dose Multiple Dose	 4-6 >6	 3-5 3-5
Comparative Oral Dose Single Dose Multiple Dose	 10mg 1mg?	 10mg 10mg

Following single dose therapy with methadone, the duration of methadone's analgesic effect is 4-6 hours and is determined primarily by its rapid distribution into tissues such as the lung, liver, spleen and kidney.[4] With chronic administration, accumulation of methadone in tissues acts as a peripheral reservoir resulting in the long elimination half-life of methadone, and a considerable increase in its duration of action.[1,4,6] Due to this prolonged half-life, frequent dose escalations (within 2-3 days) and short dosing intervals (< 6-8 hours) lead to methadone accumulation and potential adverse effects of respiratory depression and over sedation.[6]

The comparative dose equivalence of morphine and methadone is unclear. Single parenteral doses of methadone and morphine are considered equianalgesic and have an equal duration of analgesia. With multiple dosing, the cumulative effects of methadone and its longer half-life become significant to the effect that methadone has a much higher analgesic equivalence to morphine than the often quoted 1:1 ratio.[4] One reference currently uses a parenteral morphine:methadone ratio of 5:1.[5] Another text suggests that with methadone's oral bioavailability being twice that of morphine, and its duration of action up to three times that of morphine, an equivalent oral methadone dose would be at least one-sixth that of oral morphine.[7] Three case reports used an initial total dose of methadone approximately two-thirds of the total daily dose of morphine.[3] Subsequently, the dose of methadone was reduced with no loss of pain control. One case report of substituting methadone for morphine at one-tenth the total morphine dose resulted in progressive confusion, sedation, and respiratory depression necessitating naloxone administration.[5]

There is wide interpatient variation in rates of absorption and elimination of methadone, making it difficult to predict equi-analgesic doses and appropriate

intervals for administration in an individual patient. Patients with hepatic or renal dysfunction and the elderly appear more prone to the cumulative effects of methadone. It would seem prudent for the treatment of chronic cancer pain, that the initial oral 24 hour methadone dose should be no greater than 10% of the oral 24 hour morphine dose. Methadone should initially be given in divided doses every 6 to 8 hours. Exacerbation of chronic pain should be treated with short-acting narcotics (e.g. morphine, hydromorphone) on a PRN basis. The dosing interval of methadone may need to be extended as therapy continues. Dose titrations should occur slowly every 4-6 days as steady state levels are not achieved until 5 days (range 2-10 days) of therapy.[1,6]

Frequent assessments of respiratory rate, sedation scale and analgesia should be made especially during the first few weeks of therapy. Even with rigid monitoring, severe respiratory depression or over sedation may still occur necessitating temporary discontinuation of methadone with or without naloxone administration (0.1-0.2mg IV/SC).[1,4,5] Due to methadone's long elimination half-life, continuous monitoring of respiratory rate and sedation scale, and potentially repeat naloxone doses, may be required for an extended period following its discontinuation.

In summary, morphine remains the standard opioid for the treatment of chronic cancer pain and is ideal for use in patients who require rapid analgesic titration. In patients requiring escalating doses of morphine or other front-line narcotic (e.g. hydromorphone) with inadequate analgesia, or in patients intolerant of morphine (e.g. intolerable side effects or a true morphine allergy), methadone represents an alternate analgesic, but is best suited for patients whose pain is not labile and easily assessable. It is a long-acting, low cost opioid with a high bioavailability. Because of high inter-patient variability in methadone pharmacokinetics, oral methadone therapy should be initiated at a maximum of 10% of the oral morphine equivalent with adjustments in dosage taking place slowly every 4 to 6 days. Breakthrough pain medication should be ordered using a shorter duration opioid such as morphine or hydromorphone and the patient must be closely monitored for adverse effects from accumulation.

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Cotrimoxazole-Induced Hyperkalemia

Trimethoprim-sulphamethoxazole (cotrimoxazole, TMP-SMX) is a commonly used antibiotic for a variety of infections including the prevention and treatment of pneumocystis carinii pneumonia (PCP) in patients with acquired immunodeficiency syndrome (AIDS). Hyperkalemia has been recently reported as a potential

complication associated with TMP-SMX.[1-5]

Reports

a. High Dose TMP-SMX for PCP

Greenberg *et al* conducted a retrospective cohort study in which 25 hospitalized AIDS patients receiving high dose oral or IV TMP-SMX (20mg/kg/day TMP) for PCP were compared to a control group of 26 AIDS patients not receiving this drug.[3] Patients on potassium supplements or those with a serum creatinine concentration greater than 186 umol/L were excluded. Baseline serum potassium concentrations were similar in treatment and control groups (4.1mmol/L and 4.3mmol/L, respectively). Serum potassium concentrations in the TMP-SMX group increased by 1.1mmol/L compared to no change in the control group ($p<0.0001$). Serum potassium concentrations peaked at 9.8 ± 0.5 days of TMP-SMX therapy. Blood urea nitrogen (BUN) and serum creatinine concentrations also rose significantly in the TMP-SMX group.

Velazquez *et al* retrospectively studied 30 consecutive AIDS patients receiving high dose TMP-SMX (n=23) or TMP-dapsone (n=7) for PCP.[5] Average treatment duration was 5.3 ± 2.8 days. According to the investigators, patients were not receiving other medications which could elevate serum potassium concentrations. In this group of patients, serum potassium concentrations increased by an average of 0.6mmol/L during treatment despite normal adrenocortical function and glomerular filtration rate. Serum potassium concentrations exceeded 5.0mmol/L in 15 (50%) patients and decreased to pretreatment values when the drug was discontinued. Serum creatinine concentrations were higher (mean difference 15.9umol/L) during the treatment phase than at baseline.

There are 3 further case reports involving males aged 23-53 years with AIDS who received high dose TMP-SMX therapy for PCP.[1,2,4] Normal baseline serum potassium concentrations rose progressively to 5.7-7.0mmol/L by day 8-9 of therapy. One patient was receiving prednisone along with TMP-SMX.[1] In all patients, BUN and/or serum creatinine concentrations rose slightly during therapy. One patient was rechallenged with high dose TMP-SMX and hyperkalemia recurred.[2] Once the dose was reduced to 15mg/kg/day TMP, the hyperkalemia resolved promptly.

b. Standard Dose TMP-SMX

Three case reports have been published in which elderly females without AIDS (age range 72-84 years) were treated with standard doses of TMP-SMX (160mg TMP BID) for respiratory or urinary tract infections.[6] Normal baseline potassium concentrations in these patients rose to greater than 5.0mmol/L within 2-3 days of therapy and remained elevated until the drug was discontinued. All patients had normal serum creatinine concentrations during TMP-SMX therapy.

In a prospective chart review, Rajendran *et al* evaluated the effects of standard doses of TMP-SMX (TMP # 320mg/day, n=80) compared to other antibiotics (n=25) on the development of hyperkalemia.[7] In the TMP-SMX group, serum potassium concentrations increased by a mean of 1.21mmol/L with peak potassium concentrations occurring between 4 and 5 days of therapy. Peak potassium concen-trations exceeded 5.0mmol/L in 50 (62.5%) patients and 5.5mmol/L in 17 (21.2%) patients receiving TMP-SMX. Subgroup analyses evaluating age, diabetes, renal impairment and concomitant therapy with potassium-altering medications as risk factors revealed underlying renal insufficiency as the only factor associated with a significant increase in serum potassium concentration.

Proposed Mechanism

Trimethoprim has structural and chemical similarities to the potassium sparing diuretics, amiloride and triamterene.[2] It is believed that trimethoprim reversibly inhibits sodium transport across amiloride-sensitive sodium channels in the distal nephron in a dose-dependent fashion.[1-5] This appears to cause hyperpolarization of the luminal membrane and inhibition of potassium secretion which can lead to the development of hyperkalemia.

Patients with AIDS may also be more prone to hyperkalemia due to adrenal insufficiency or hyporenin and hypo-aldosterone states.[3] However, several of the reports involving AIDS patients identified that these patients had no evidence of preexisting adrenal dysfunction.[1,3-5]

Management

Discontinuation of TMP-SMX therapy appears to result in a prompt fall of serum potassium concentrations to pretreatment levels within 2 days (range 1-5 days). Only 3 of 23 patients who developed hyperkalemia in the cited reports were treated with sodium polystyrene sulfonate (Kayexalate®) to reduce potassium concentrations.[1,3,6] The management of hyperkalemia was not reported in the study by Rajendran *et al*.[7] There was no mention of abnormal ECGs in any of the reports.

Conclusions

Reversible hyperkalemia secondary to TMP-SMX therapy has been increasingly reported. This appears to occur more commonly in patients with AIDS treated with high dose therapy; however, this condition has also been reported with conventional doses used in non-AIDS patients who are elderly or have underlying renal impairment. Serum potassium concentrations appear to progressively increase with peak values occurring as early as 4-5 days (range 2-9 days) after initiation of therapy. TMP is believed to be responsible for hyperkalemia due to blockade of amiloride-sensitive sodium channels. A decline in serum potassium concentrations to pretreatment levels occurs within a few days after TMP-SMX therapy is discontinued.

Patients at risk for significant elevations of serum potassium concentrations from TMP-SMX therapy should be monitored closely; these include patients treated with high dose therapy and those with renal insufficiency.

References

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Adverse Drug Reaction Report (ADR) 1995

There were a total of 28 suspected ADRs reported in 1995:

Drug	Suspected ADR (# pts)
Captopril	facial angioedema (1)
Carbamazepine	respiratory distress (1)
Cisapride	tachycardia, hypertension (1) hallucinations (1)

Clindamycin	rash (1)
Cloxacillin	renal impairment (2)
Cotrimoxazole	hyperkalemia (3) rash, total body (1)
Cyclophosphamide	hypersensitivity (1)
Dapsone	methemoglobinemia (1)
Diltiazem	rash (1)
Hydrochlorothiazide	pulmonary edema (1)
Ibuprofen	facial angioedema (1)
Imipenem	seizure (1)
Indocyanine green	rash (1)
Ketoconazole	rash (1)
Methotrimeprazine	laryngospasm/neck spasm (1)
Nifedipine	gynecomastia (1)
Paroxetine	hyponatremia (1)
Phenytoin	rash (1)
Ranitidine	rash (1)
Risperidone	hyperthermia (1)
Spironolactone	hypersensitivity (1)
Vancomycin	neutropenia (1) renal impairment (1)

The continued reporting of all suspected ADRs by nurses, physicians and pharmacists aids in the determination of the incidence of adverse events.

To notify Pharmacy of an ADR, either fill out a yellow ADR alert card, available on all nursing units, and send to pharmacy, or call the pharmacy at local 62481 (12 & Oak site) or local 7249 (UBC site). Pharmacists complete all ADR forms and forward copies to the BC Drug and Poison Information Centre (DPIC). DPIC then forwards all reports to the Canadian ADR program in Ottawa for collation. Your continued support of the ADR program is greatly appreciated.

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