SULTANATE OF OMAN
MINISTRY OF HEALTH

PHARMACEUTICAL NEWSLETTER

In this issue:

ARTICLE REVIEW

01. Room temperature Storage of Medications Labeled for Refrigeration

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(Article from the American Journal of Health-System Pharmacy)
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Abstract

Purpose: Data regarding the recommended maximum duration that refrigerated medications available in hospital pharmacies may be stored safely at room temperature were collected and compiled in a tabular format.
Methods: The prescribing information for medications labeled for refrigeration as obtained from the supplier were reviewed for data addressing room-temperature storage. Telephone surveys of the products' manufacturers were conducted when this information was not available in the prescribing information. Medications were included in the review if they were labeled to be stored at 2-8 °C and purchased by the pharmacy department for uses indicated on the hospital formulary. Frozen antibiotics thawed in the refrigerator and extemporaneously compounded medications were excluded. The *U.S. Pharmacopeia's* definition of room temperature (20-25 °C) was used for this review.

Results: Of the 189 medications listed in *AHFS Drug Information 2006* for storage in a refrigerator, some present medications were included in this review. The table may help to avoid unnecessary drug loss and expenditures due to improper storage temperatures.

Conclusion: Information regarding the room-temperature storage of medications labeled for refrigerated storage was compiled.

Introduction

The U.S. Pharmacopeia's Med-marx medication-error-reporting system has received nearly 1000 reports involving errors associated with refrigerated medications. Many of these reports were a result of nursing staff not realizing that certain medications required refrigeration. Subsequent errors involved delayed administration of medications to patients and inappropriate storage of expensive medications (e.g., epoetin alfa). Recommendations based on a review of these errors suggested displaying a table on the outside of the refrigerator door listing common refrigerated items for that particular unit.

Inappropriate vaccine storage has been implicated in numerous reports of vaccine-related adverse events. For example, two days after receiving a pneumococcal polysaccharide vaccination that had not been refrigerated, a patient developed dizziness, racing heart, jerking of the limbs, and "pins and needles" from head to toe, resulting in a persistent and significant disability. In another case, a patient developed a cluster of 20 painful and itchy vesicles on an erythematous base on the midposterior lateral forearm after receiving varicella vaccine that was not properly refrigerated.

In 1975, Wolfert and Cox recognized that pharmacists were often asked about the stability of refrigerated medications that are accidentally stored at room-temperature. However, because product labeling was insufficient regarding room-temperature stability and pharmacists were not routinely able to predict stability based on the physicochemical properties of the medications, the authors surveyed manufacturers about room-temperature storage of selected medications labeled for refrigeration. This information was then compiled into a table for use as a guide to control drug storage within the authors' institution.

In 1983, Vogenberg and Souney compiled a similar table describing the acceptable duration of storage of medications labeled for refrigeration when refrigerated (2-8 °C) after 24 hours of storage at room-temperature, when stored in a cool place (8-15 °C), and when stored at room-temperature (15-30 °C).

In 1987, Sterchele described the frequency of drug information requests received concerning room-temperature storage of drug products labeled for refrigeration. The author reported that this information was not easily retrievable and often incomplete and compiled an updated table to supplement the previously available information on the topic. Only 22 of 36 manufacturers replied with information about 39 products, and most manufacturers did not provide data for storage in "a cool place," as it was unrecognized as a method for storage.

In 1990, Dalton-Bunnow and Halvachs updated the available data. In 2006, Cobos Campos et al. compiled written information from drug manufacturers about the room-temperature storage of 83 medications labeled for refrigeration. This information was limited by the fact that it was collected outside of the United States and published in the Spanish medical literature.

The objective of this study was to provide an updated table of the maximum acceptable duration that medications labeled for refrigeration may be stored at room-temperature.

Table: Acceptable Duration of Room-Temperature Storage (20-25 °C) for Medications Labeled for Refrigeration

Drug Product	Brand Name (Manufacturer)	Acceptable duration of storage at room temp.
Alprostadil injection	Prostin VR Pediatric (Silcor)	34 days at 20 °C 26 days at 30 °C
Botulinum toxin type-A 100 units	Botox (Allergan)	5 days

Calcitonin injection	Miacalcin (Novartis)	14 days
Calcitonin nasal spray	Miacalcin (Novartis)	35 days
Calcitonin salmon intranasal	Fortical (Upsher-Smith)	7 days
Candida albicans skin test	Candin (Allermed Laboratories)	7 days
Cisatracurium injection	Nimbex (Abbott)	21 days
Conjugated estrogens injection	Premarin IV (Wyeth)	7 days
Darbepoetin alfa	Aranesp (Amgen)	7 days
Digoxin immune fab (ovine)	Digibind (GlaxoSmithKline)	30 days
Diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B	Pediarix (GlaxoSmithKline)	24 hr
Diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed	Infanrix (GlaxoSmithKline)	72 hr
Epoetin alfa multidose	Procrit (Ortho Biotech)	7 days
Eptifibatide 2 mg/mL	Integrilin (Schering)	60 days
Etanercept prefilled syringe	Enbrel (Immunex Corporation [Amgen and Wyeth Pharmaceuticals])	4 days
Famotidine	Pepcid (Bedford)	3 mo
Filgrastim vials	Neupogen (Amgen)	7 days
Fosphenytoin sodium injection	Cerebyx (Pfizer)	48 hr
Hepatitis A vaccine, inactivated	Havrix (GlaxoSmithKline)	72 hr
Hepatitis B immune globulin (human)	Hyperhep B S/D (Bayer)	Cumulative exposure for 7 days
Hepatitis B vaccine (recombinant)	Engerix-B (GlaxoSmithKline)	72 hr
Immune globulin (human)	Gamastan S/D (Bayer)	Cumulative exposure for 7 days
Influenza virus vaccine	Fluarix (GlaxoSmithKline)	72 hr
Insulin as part (rDNA origin) injection	Novolog (Novo Nordisk)	28 days
70% insulin aspart protamine suspension and 30% insulin	Novolog Mix 70/30 pen fill cartridge (Novo Nordisk)	14 days
70% insulin aspart protamine suspension and 30% insulin	Novolog Mix 70/30 vial (Novo Nordisk)	28 days
Lente human insulin (rDNA origin) zinc	Humulin L (Lilly)	28 days
NPH, human insulin isophane suspension	Novolin N vial (Novo Nordisk)	30 days
Regular human insulin injection (rDNA origin)	Novolin R vial (Novo Nordisk)	30 days
Humulin Ultralente human insulin (rDNA origin) extended zinc suspension	Humulin U (Lilly)	28 days

Hyaluronic acid	Healon (AMO Advanced Medical Optics)	14 days
Interferon beta-1a i.m. injection	Avonex (Biogen Idec)	30 days
Interferon beta-1a s.c. injection	Rebif (Serono)	30 days
Lopinavir/ritonavir capsules	Kaletra capsules (Abbott)	60 days
Lopinavir/ritonavir oral solution	Kaletra solution (Abbott)	60 days
Melphalan 2-mg tablets	Alkeran (GlaxoSmithKline)	7 days
Methylergonovine maleate injection	Methergine (Novartis)	14 days
Neomycin sulfate-polymixin B sulfate solution for irrigation	Neosporin G.U.Irrigant Sterile (Monarch Pharmaceuticals)	6 mo if undiluted
Octreotide acetate injectable suspension	Sandostatin (Novartis)	14 days
Palivizumab powder and solution	Synagis (MedImmune)	14 days
Peg-interferon alfa-2a vial	Pegasys vial (Roche)	14 days
Peg-interferon alfa-2a vial prefilled syringe	Pegasys prefilled syringe (Roche)	6 days
Penicillin G benzathine & penicillin G procaine injection suspension	Bicillin CR (Wyeth)	7 days at 25 °C 1 day at 40 °C
Pneumococcal 7-valent conjugate vaccine (diphtheria CRM_{197} protein)	Prevnar (Wyeth)z	7 days
Quinupristin-dalfopristin injection	Synercid (DSM Pharmaceuticals)	7 days
Rabies immune globulin (human)	Hyperab S/D (Talecris)	7 days
Rabies vaccine	Rabavert (Chiron)	6.2% loss after 12 months
Ritonovir capsules	Norvir (Abbott)	30 days
Rh_oD immune globulin (human)	Hyperrho SD (Bayer)	Cumulative exposure for 7 days
Rocuronium bromide	Zemuron (Organon USA)	60 days
Saquinavir soft gelatin capsules	Fortovase (Roche)	90 days
Succinylcholine chloride multidose	Anectine (GlaxoSmithKline)	14 days
Tetanus immune globulin human	Hypertet S/D (Talecris)	7 days
Tipranavir capsules	Aptivus capsules (Boehringer-Ingel.)	60 days if opened
Tobramycin inhalation solution	Tobi (Chiron)	28 days
Trifluridine ophthalmic solution	Viroptic (Monarch Pharmaceuticals)	14 days
Vinorelbine tartrate injection	Navelbine (Pierre Pharmaceuticals)	72 hr
Vitamin A	Aquasol-A parenteral (Aai Pharma/Mayne)	28 days

NEWS

01. MHRA advises on erythropoietins

New prescribing advice for recombinant human erythropoietins is highlighted in the December 2007 issue of the Medicines and Healthcare products Regulatory Agency's *Drug Safety Update*.

Recombinant human erythropoietins (epoetins) are indicated for the treatment of anaemia in patients with chronic renal disease and for treating patients with non-myeloid cancer who develop anaemia after chemotherapy.

The new advice warns that overcorrection of haemoglobin concentration in patients with chronic renal disease may increase the risk of death and serious cardiovascular events and, in patients with cancer, may increase the risk of thrombosis. "Recombinant human erythropoietins should not be given to patients with cancer who do not fulfil the criteria in the authorised cancer indications," it says.

The update also highlights measures to minimise the risk of overdose with dosulepin and to discourage its use for new patients. It explains that pack sizes have been limited and child resistant blister packs introduced.

Two safety issues relating to the use of medicines during pregnancy are also included. Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists should not be used during any stage of pregnancy. Their use by women who are planning pregnancy should be avoided unless absolutely necessary, it says.

In addition, updated safety information has been issued for mycophenolate mofetil (Cellcept) relating to congenital malformations after use during pregnancy.

Finally, the update warns about the risks of myocardial ischaemia with short-acting beta agonists. It says that patients with a history of, or risk factors for, heart disease should not be given beta agonists for management of premature labour. In addition, these patients should be alert to symptoms of worsening heart disease if taking beta agonists for respiratory disease.

Ref: The Pharmaceutical Journal (Vol 279) 8 Dec 2007

02. Parents rate honey for children's night-time cough

Parents rated honey, but not dextro-methorphan, as better than no treatment for relieving nocturnal cough in children in a US study published recently (*Archives of Pediatrics and Adolescent Medicine* 2007;161:1140). The study involved 105 children aged two to 18 years with upper respiratory tract infections and nocturnal symptoms. The children were randomised to receive a single dose of buckwheat honey, honey flavoured dextromethorphan or no treatment, 30 minutes before bedtime.

In a survey of cough symptoms and sleep difficulty before and after treatment, parents ranked honey as best and no treatment as worst. However, direct comparisons between honey and dextromethorphan did not show any significant differences.

"While additional studies to confirm our findings should be encouraged, each clinician should consider the findings for honey, the absence of such published findings for dextromethorphan, and the potential for adverse effects and cumulative costs associated with the use of dextromethorphan when recommending treatment for families," the researchers conclude.

However, they highlight the risk of infantile botulism when children younger than one year are given honey to eat and the rare risk of grayanotoxin-mediated syndrome.

Ref: The Pharmaceutical Journal (Vol 279) 15 Dec 2007

REPORTS ON INDIVIDUAL DRUGS

01. Fluconazole reasonable alternative to griseofulvin

Fluconazole is a reasonable alternative to griseofulvin for treating scalp ringworm in children, according to the December issue of the *Drug and Therapeutics Bulletin*.

In an update to previous advice issued in 1996, which recommended griseofulvin, the *DTB* says that evidence indicates the newer antifungals — terbinafine, fluconazole and itraconazole — are as effective and as well tolerated as griseofulvin, but require shorter treatment courses.

Terbinafine is increasingly recommended as first-line treatment for the most common cause of scalp ringworm infection in the UK and is the cheapest option, says the *DTB*.

However, the bulletin raises concerns that it has not been licensed for children despite evidence of its effectiveness and that a suitable formulation is not available. Similarly, itraconazole is only available in 100mg capsules, making it difficult to use on a dose per weight basis, it says. In contrast, fluconazole is available as a powder for oral suspension as well as capsules and seems a reasonable alternative, it says.

The bulletin also highlights that topical antifungals are generally considered inadequate sole treatments for scalp ringworm but can be used as an adjunct to oral therapy.

The December *DTB* also reviews the effectiveness and safety of steroids for bacterial meningitis in children.

It concludes that it is reasonable, on current information, to give dexamethasone initially to any child older than one month presenting with bacterial meningitis who does not have a rash suggestive of meningococcal disease. This is because the infection could be due to *Haemophilus influenzae b*, for which there is evidence that treatment prevents hearing loss.

Ref: The Pharmaceutical Journal (Vol 279) 8 Dec 2007

02. Omalizumab approved for allergic asthma sufferers

People with unstable allergic asthma could now be eligible to receive omalizumab (Xolair), with the launch of new guidance by the National Institute for Health and Clinical Excellence. Omalizumab is a recombinant humanised monoclonal antibody that inhibits the binding of IgE to high affinity receptors on the surface of mast cells and basophils, preventing the release of inflammatory mediators and reducing allergen-induced airway reactions.

NICE has approved the drug as an add-on to optimised standard therapy in the treatment of severe persistent IgE-mediated asthma in adults and adolescents (12 years and older) whose condition is unstable — involving several exacerbations as well as visits to hospital. Optimised standard therapy, NICE says, should include a trial of inhaled high-dose corticosteroids and long-acting beta$_2$ agonists, as well as leukotriene receptor antagonists, theophyllines, oral corticosteroids, beta$_2$ agonist tablets and smoking cessation.

Therapy should only be started if the patient has IgE-mediated allergy confirmed by clinical history and allergy skin testing.

Corticosteroids in asthma: Children under the age of 12 years requiring inhaled corticosteroid treatment for asthma should be treated with the least costly product that is suitable for them, NICE has also recommended.

The new guidance stipulates that a combination product can be used if both inhaled corticosteroid and long-acting beta2 agonist treatment is required, but the choice of whether to prescribe a combination product or two separate inhalers should be made on an individual basis.

Ref: The Pharmaceutical Journal (Vol 279) 1 Dec 2007

DRUG REACTIONS

01. Lumiracoxib
Risk of serious hepatotoxicity

Lumiracoxib (Prexige), is a COX-2 selective non-steroidal anti-inflammatory drug (NSAID) used to treat painful symptoms of osteoarthritis of the knee and hip at a dose of 100 mg once daily. It is approved in more than 50 countries worldwide and was first launched in Brazil in 2005. Concern was raised worldwide after rare reports of serious liver reactions, mostly relating to daily doses that were higher than licensed for use in osteoarthritis. Some post-marketing reports of severe hepatic adverse effects have been reported in some countries around the world. Some countries have reacted with specific regulatory measures:

Australia (1). In August 2007 Australia's Therapeutic Goods Administration (TGA) cancelled the registration of lumiracoxib due to reports of serious liver adverse effects associated with the use of the drug.

As of 10 August last year, the TGA had received eight reports of serious liver adverse reactions related to lumiracoxib, including two deaths and two liver transplants. These reports were "urgently investigated" by the TGA and its expert advisory committee, the Adverse Drug Reactions Advisory Committee (ADRAC). ADRAC subsequently recommended the cancellation of registration for lumiracoxib, "due to the severity of the reported side effects associated with this drug". The TGA is advising patients to discontinue lumiracoxib use immediately, and to discuss alternative treatments with their physician.

Canada (2). Health Canada has reviewed all safety and *efficacy* data for lumiracoxib from Novartis and has concluded that the risk of serious hepatotoxicity associated with the use of lumiracoxib cannot be safely and effectively managed. Health Canada has thus requested that Novartis stop the sale of lumiracoxib in Canada. Consistent with this decision to cease sales and marketing of lumiracoxib, Novartis is asking Canadian pharmacists and distributors to return the product to the company. Patients taking. lumiracoxib have been advised to discontinue its intake and contact their physician for advice about alternative therapies.

Prescribers are advised:

- not to initiate treatment of new patients;
- to advise patients to discontinue lumiracoxib;
- to review treatment options for patients currently taking lumiracoxib.

Pharmacists are advised:

- not to dispense further prescriptions for lumiracoxib;
- to tell patients to discontinue lumiracoxib and contact their physician if they have any concerns.

Consumers are advised to return the product to their pharmacy.

New Zealand (3). The regulatory agency has withdrawn the market authorization for 200 mg and 400 mg lumiracoxib tablets for acute use, but kept the licenses of 100 mg once daily for osteoarthritis.

Turkey (4). Turkey has suspended the marketing authorization for 100 mg lumiracoxib tablets pending further review.

United Kingdom (5). Concern was raised worldwide after rare reports of serious liver reactions mostly relating to daily doses of lumiracoxib that are higher than licensed in the EU. Following consultation with the MHRA and other European regulators, the manufacturer of the osteoarthritis drug, lumiracoxib (Prexige), has written to health professionals to inform them of new restrictions on the prescribing of lumiracoxib.

A summary of the latest advice from MHRA includes the following:

Lumiracoxib should not be used in patients with current or past liver disease, those taking other medicines that may cause liver problems, or who have had previous drug-induced liver reactions.

Blood tests to check liver function are needed before treatment, at monthly intervals during treatment, and at any stage if patients are unwell with possible liver problems. Patients already taking lumiracoxib should have their treatment reviewed at the next convenient opportunity. Blood tests should be taken if continued treatment is considered appropriate. Do not exceed 100 mg once daily and use only for the shortest duration necessary to control symptoms.

Reports in WHO database

Hepatic function abnormal - 3

Ref: WHO Pharmaceuticals Newsletter No.5, 2007

02. PDE5 Inhibitors Reports of sudden decreases in or loss of hearing

USA. The US FDA informed healthcare professionals of reports of sudden decrease in, or loss of hearing following the use of phosphodiesterase type 5 enzyme (PDE5) inhibitors sildenafil (Viagra), vardenafil (Levitra), tadalafil (Cialis) for the treatment of erectile dysfunction, and sildenafil citrate (Revatio) for the treatment of pulmonary arterial hypertension. In some cases, the sudden hearing loss was accompanied by tinnitus and dizziness. Medical follow-up on these reports was often limited, which makes it difficult to determine if the loss of hearing was related to the use of one of the drugs, an underlying medical condition or other risk factors for hearing loss, a combination of these factors or other factors. The PRECAUTIONS and ADVERSE REACTIONS sections of the approved product labelling for Viagra, Levitra, and Cialis were revised. FDA is working with the manufacturer to revise the labelling for Revatio.

Ref: WHO Pharmaceuticals Newsletter No.5, 2007

DGPA&DC ACTIVITIES

01. DGPA&DC - An overview of the activities

(1) Pharmacy Department

The Pharmacy Department is responsible for the licensing and inspection of pharmaceutical establishments and personnel. The department conducts licensing examination every month. The following table shows the number of private pharmacies and medical stores that are licensed as on 31.12.2007 and also those cancelled in 2007:

Private Pharmacies

1	Total private pharmacies	350
2	Pharmacies opened in 2007	29
3	Pharmacies cancelled in 2007	20

Medical Stores

1	Total medical stores	40
2	Medical stores opened in 2007	6
3	Medical stores cancelled in 2007	0

As on 31.12.2007, there were 682 registered Pharmacists and 318 Assistant Pharmacists in the country.

The summary of the licensing examinations (both written and oral) conducted by the department during 2007 is mentioned below together with information about those passed and failed.

	Pharm-acists	Asst. Pharm-acists	Med. Reps	Indl. Pharma-cists
WRITTEN				
Appeared for written test	209	138	No written test for MR	9
PASS	97	66		8
FAIL	112	72		1
ORAL				
Appeared for the Oral test	186	125	26	8
PASS	82	41	19	8
FAIL	104	84	7	-

The Pharmaceutical Violation Committee, which deals with violations committed by

the establishments as well as its personnel has taken the following disciplinary actions during 2007:

Type of Est.	No. of pharmaceutical est.	Issued warning	Imposed fine ranging from 150 to 500 RO.	Withdrawn establishment licence	Withdrawn Pharmacist Licence	Ordered to close temporary
Pharmacies	13	2	11	0	0	0
Med. Store	1	1	0	0	0	1 (1 month)
Total	14	3	11	0	0	0

(2) Drug Control Department

The Drug Control Department deals with the registration of pharmaceutical companies and products, drug clearance and dangerous drugs monitoring.

The following table shows the companies and products which are registered and also those rejected in 2007.

1	No. of companies registered in 2007	67
2	No. of company registration applications rejected in 2007	7
3	Products registered in 2007	109
4	Product registration applications rejected in 2007	31

As on 31.12.2007, a total number of 379 pharmaceutical manufacturers were registered in Oman. Similarly, at the end of 2007, 4203 products were registered from those companies.

Errors are everywhere and it seems that everyone makes them. "To err is human..." as the famous idiom goes, they are unintentional as well, these can be seen as unfortunate events and can be turned into opportunities to prevent future errors. Handwritten prescriptions result in doubt between two medications that have similar names. Name mix-ups account for more than one-third of the medication dispensing errors as per studies. This is to bring to your notice a pair of names which resulted in such an error:

Sporinex - Tinidazole

Sporanox – Itraconazole

The Newsletter intends to put series of such confusing / look alike names in the issues to follow.

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