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Active Mycobacterium Infection Due to Intramuscular BCG Administration Following Multi-Steps Medication Errors

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ABSTRACT

Bacillus Calmette-Guérin (BCG) is indicated for treatment of primary or relapsing flat urothelial cell carcinoma in situ (CIS) of the urinary bladder. Disseminated infectious complications occasionally occur due to BCG as a vaccine and intravesical therapy. Intramuscular (IM) or Intravenous (IV) administrations of BCG are rare medication errors which are more probable to produce systemic infections. This report presents 13 years old case that several steps medication errors occurred consequently from physician handwriting, pharmacy dispensing, nursing administration and patient family. The physician wrote βHCG instead of HCG in the prescription. βHCG was read as BCG by the pharmacy staff and 6 vials of intravesical BCG were administered IM twice a week for 3 consecutive weeks. The patient experienced fever and chills after each injection, but he was admitted 2 months after first IM administration of BCG with fever and pancytopenia. Unfortunately four month after using drug, during second admission duo to cellulitis at the sites of BCG injection the physicians diagnosed the medication error. Using handwritten prescription and inappropriate abbreviations, spending inadequate time for taking a brief medical history in pharmacy, lack of verifying name, dose and wrote before medication administration and lack of considering medication error as an important differential diagnosis had roles to occur this multi-steps medication error.

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Introduction

Bacillus Calmette-Guerin (BCG), a live attenuated form of Mycobacterium bovis, is the most commonly used agent for intravesical therapy for patients with bladder cancer (1-5). Although the exact mechanism of its antitumor action is unknown, intravesical instillation of BCG triggers a variety of local immune responses which appear to correlate with antitumor activity (6-8). There are two major categories of adverse reactions to BCG vaccination: non-infectious and infectious. The exact incidence of adverse reactions is difficult to estimate as their definitions are not universally accepted. Rates vary between regions and centers, but local adverse reactions usually occur at a rate of 0.1 to 0.5 per 1000 vaccinations, and serious, disseminated complications occur at a rate of less than 1 in a million vaccinations (9**).**

BCG is typically instilled into the bladder weekly for six weeks. Each dose consists of a vial of reconstituted Theracys (81 mg) or one 2 mL ampoule of TICE BCG (50 mg), plus 50 mL of sterile saline injected into the bladder through a catheter and retained for two hours.

To diminish the risk of systemic infection, intravesical BCG should not be administered to patients with traumatic catheterization, active cystitis, or persistent

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gross hematuria following transurethral resection of bladder tumor (TURBT) (10).

BCG is used far less for immunotherapy than as a vaccine against tuberculosis, the incidence of infectious complications is very much higher when used in immunotherapy than when used as a vaccine (12,13). This therapeutic procedure is associated with a relatively high incidence of complications. Cystitis is very common and is regarded as an unavoidable effect of the treatment. Transient fever occurs in 3% of patients but may be due to hypersensitivity rather than systemic infection. Disseminated, life threatening infection occurs in 0.4% of patients and often causes cardiovascular instability, which may lead to collapse. It is not clear whether this instability is due to anaphylactic hypersensitivity reactions or adrenal dysfunction, or both (14).

Pneumonitis, granulomatous hepatitis or arthralgia occurs in about 0.7% of patients. They are generally regarded as manifestations of hypersensitivity, but in one case of granulomatous hepatitis, acid fast bacilli were seen in the liver tissue on microscopy and mycobacterial DNA was detected by the polymerase chain reaction (15).

Dispensing medication is the core function of pharmaceutical care and approximately 900 million medicines are dispensed each year by community and hospital pharmacies across England and Wales (16). Dispensing is a complex process unequivocally under the supervision of the pharmacist (17). Traditionally, dispensing has involved pharmacy staff manually selecting medication from shelves, transferring the correct number of medication dose units to a container and/or labeling the assembled product (18).

The most common types of un-prevented and prevented dispensing incidents were supply of the wrong drug, strength, form and quantity, and labeling medication with the incorrect directions. Factors subjectively reported by pharmacy staff as contributing to dispensing errors were workload, staffing, look-alike sound-alike drugs, interchanging formulations and computer selection errors resulting from unclear presentation of drug-selection lists on computer software (19).

Errors can arise at any stage during the dispensing process. It is estimated that each year 134 341 dispensing errors occur in community pharmacies in England and Wales (16). The majority (85%) of these errors are detected by pharmacists before the medication is supplied to the patient. However, some errors are undetected and may cause serious patient harm and occasionally death (20-22). Thus it is imperative that pharmacists review data on dispensing errors so that risk-reduction strategies are developed to safeguard the quality and safety of patient care (21).

Dispensing errors are a major concern for the pharmacy profession and occurred in community and hospital pharmacy and most commonly involved supply of the wrong drug, strength and form of medication. High workload, interruptions and inadequate lighting were both subjectively and objectively reported as contributing to dispensing errors (19).

Treatments of complications of the intravesical instillation of BCG have been reviewed (17, 18, 24). Transient fevers exceeding 38.5°C are not treated specifically but isoniazid (300 mg daily) is given for three months if the fever lasts over 12 hours. In either case BCG therapy is withheld but resumed when symptoms have resolved. Hypersensitivity reactions are likewise treated with isoniazid (300 mg daily) for three months and BCG therapy is resumed only if benefits exceed risks.

The IRP (isoniazid-rifampicin-prednisolone) regimen has been advocated for acute severe illnesses and suspected or definite generalized infection, particularly if there are cardiovascular symptoms or signs (14, 25). This regimen consists of isoniazid 300 mg and rifampicin 600 mg daily for six months and prednisolone 40 mg intravenously daily until symptoms subside.

BCG should not be administered I.V., SQ, or Intradermal. In fact it should be considered as a biohazard agent. Its labeling contains a Warning: “Use appropriate precautions for handling and disposal” and proper preparation technique, handling, and disposal of all equipment in contact with BCG as a biohazard material are recommended. BCG infections have been reported in healthcare workers due to accidental exposure (needle stick, skin laceration). Nosocomial infections have been reported in patients receiving parenteral medications prepared in areas where BCG was prepared. To avoid cross contamination, do not prepare parenteral medications in an area where BCG has been prepared (25).

This case could be considered one of a rare case that several errors occurred concomitantly in subsequent steps from prescription writing to dispensing drug and administration of it. Finally diagnosis of the patient problem as a harmful consequence of a medication error had delayed. Careful analysis of these items also can lead healthcare professional to consider some important points for prevention of these kinds of medication errors.

Case report

A 13 years old boy with some problems history in his sexual maturation was visited with an urologist. The patient was also known a case of bladder dystrophy and was subject to surgical treatment for several times before his new problem. Six ampoules of HCG (human chorionic gonadotropin) were ordered for him, but physician wrote βHCG instead of HCG in the prescription. βHCG is the name of the laboratory test which is routinely used for confirmation of pregnancy. βHCG was read as BCG by the pharmacy staff and 6 ampoules of intravesical BCG (120 mg of live mycobacterium bovis Pasteur strain 1173P2 produced by Pasteur Institute of Iran) were supplied to

patient. Routinely six vials of intravesical BCG is the usual course of treatment when it is used for bladder cancer. Unfortunately following this medication error, six ampoules of intravesical BCG were administered intramuscularly twice a week for 3 consecutive weeks. The patient experienced fever and chills after the first injection, but he and his family thought that these symptoms are usual phenomenon after receiving this kind of medication. So he continued to use his drug until all of them consumed. About two months after beginning of drug administration the patients was visited by a physician and then he presented to a central pediatric hospital. At the time of admission he was pancytopenic, anemic and febrile (39°c). In his lab-tests RBC, WBC and platelet counts were 2.8*10^6/mm^3, 2700/mm^3 and 92000/mm^3 respectively and he had Hb level of 7 grams/dl[3]. His AST and ALT were 80 U/L and 46 U/L and he had ESR[1] and Cr[2] level 40 mm/h and 1.4 mg/dl respectively. Urine analysis revealed a lot of bacteria and WBC in his urine sample. His liver sonography was normal but spleen was enlarged and kidneys showed signs of hydronephrosis. Accumulation of fluid was apparent around his liver. Even to this time did not diagnose any relationship between a medication error and clinical signs of the patients were made. He referred to an oncologist and bone marrow aspiration and pathologic investigation were ordered for differential diagnosis of pancytopenia but the result was not indicative of any abnormality. After ten days of admission he was discharged from the hospital with good general condition and recommended to see a nephrologist and an infectious disease specialist for further investigation and follow up.

About two months after discharge he came back to the hospital, due to cellulitis at the sites of BCG injection. His chief complaint was erythema and swelling of gluteal region mainly at the left side with tenderness and pain radiating to left inguinal region. In this time medical staff guessed a relationship between medication errors and problems of the patients. The patients had pruritus and had no fever. Sonography of the gluteal and inguinal region showed edema and inflammation and swollen lymph nodes. After suspicion to mycobacterium infection, a skin biopsy in gluteal region performed and pathologic investigation showed poorly formed granuloma, composed of epithelioid histocytes that surrounded by lymphocytes and multinucleated giant cells. No caseous necrosis was noted but the overlying epidermis showed spongiosis and lymphocytic exocytosis with PMN infiltration in the dermis. After surgical operation on his lesion, anti-tuberculosis medications were considered for him. Isoniazid 300mg, ethambutol 450mg and rifampin 300mg daily were started during the hospital stay and continued after discharge to 6 month.

Follow up the patients for one year showed that the reported case was responded to the treatment very good and he had not any signs of systemic consequences of infection.

1 Erythrocyte sedimentation rate
2 Creatinine

Discussion

Intravesical BCG is the most efficacious agent for non-muscle invasive bladder cancer. BCG therapy has been shown to delay (although not necessarily prevent) tumor progression to a more advanced stage, decrease the need for subsequent cystectomy, and improve overall survival. In a systematic review, the activity of intravesical BCG was analyzed in six randomized trials that included 585 eligible patients with Ta or T1 disease (26). Those treated with Transurethral resection of bladder tumor (TURBT) plus BCG had significantly fewer recurrences at 12 months compared to those managed with TURBT alone (odds ratio 0.30; 95% CI 0.21-0.43).

Our reported patient is one of a few cases who received multiple IM injections of intravesical BCG and it seems that he is the first case who had been subject for 6 doses IM administration as twice a week. Same as other reported cases, fortunately this case was adequately responded to anti-tuberculosis chemotherapy.

A review of over 5000 publications worldwide on BCG between 1980 and 1995 revealed 28 four adults cases of disseminated disease due to BCG. Twenty-four patients had AIDS or various congenital immune defects and, despite anti-tuberculosis chemotherapy, 20 died. The remaining four patients had no evident immunosuppression; they received various anti-tuberculosis drug regimens and all survived (27).

There are also some case reports of disseminated BCG infection following intravesical administration of BCG (28).

Disseminated disease is treated in a similar manner as tuberculosis due to virulent M. bovis, with rifampicin and isoniazid and a third drug selected from ethambutol, ethionamide, and streptomycin. Pyrazinamide is not used to treat M. bovis infection, because it is naturally resistant to this agent. It may be necessary to continue treatment for longer than the usual six month period in immunocompromised patients and adverse drug reactions and interactions may occur, particularly in those with AIDS (11).

Few cases of inadvertent IM or IV administration of BCG have been reported. In one case following IV administration of BCG, sepsis and systemic infection happened which was successfully treated with anti-tuberculosis medications including isoniazid, rifampicin, ethambutol and methyl prednisolone (29). In another case in which four doses of BCG which has been prescribed for intravesical use in a patient, inadvertent intramuscular use caused headache, sweating and fever. Three days after administration this patient experienced pain and indurations in the site of injections and severe pain in the hypogastric area. Although this patient didn't show clear

sign of active systemic infection and CXR revealed no sign in consistent with involvement of respiratory system, a prophylactic course of anti-tuberculosis medications consisting of isoniazid and rifampin administered for the patient (30).

There is also another case report about a patient in whom inadvertent intramuscular injection of BCG vaccine into an already tuberculin-sensitive individual resulted in a severe and prolonged local reaction. In this case healing appeared to be hastened by anti-tuberculosis chemotherapy (31).

Analysis of this patient as a medication error case, reveal some important points which could help us preventing such potentially hazardous errors and their dangerous outcomes.

Medication errors are among the most common medical errors, harming at least 1.5 million people every year (32). Medication errors include prescribing errors, dispensing errors, medication administration errors, and patient compliance errors (33).

Error management has two components: limiting incidents and creating systems that are better able to tolerate the occurrence of errors (34).

Of these items it seems that the most important factors that played role in happening this medication error was:

- Using handwritten prescription, which lead pharmacy staff to misread the prescription and faulty dispensing and is prohibited in many developed countries. Prescribers with poor handwriting should print or type medication or prescription orders if direct order entry capabilities for computerized systems are unavailable. A handwritten order should be completely readable (not merely recognizable through familiarity). An illegible handwritten order should be regarded as a potential error. If it leads to an error of occurrence (that is, the error actually reaches the patient), it should be regarded as a prescribing error.

- Using inappropriate abbreviations in prescribing (βHCG instead of HCG)

- Labeling error (the medication used by the mentioned patient, lacking complete information on its label so it was impossible for administrator to check for identity of the drug and proper way of its administration). Of course BCG vial had a unique package with an aluminum foil cover that was questionable for nursing staff.

- Spending inadequate time for asking about disease which the prescription is written for and taking a brief medical history from the patient.

- It is important before administration of any drug especially potentially hazardous agents, administrator should be assured that the dispensed medication and the written medication in the prescription is the same. This will necessitate using appropriate labeling system on containers and packaging of the drug formulations. Injectable drugs have more importance with respect to this item.

- Unbelievably sometimes a series of sequential errors could surpass our defense mechanism aiming to prevent errors. In our case using improper abbreviation by the physician caused pharmacy staff to misread the prescription, an error which could be prevented by taking a brief history of the patient. Instead of this approach pharmacy staff relied on their guess that the number of vials in the prescription is in concordance with the number of intravesical BCG routinely used in a course of BCG therapy. So they translated the erroneous abbreviation used by the physician βHCG to BCG while the physician meant HCG to be used for the patients.

- All drug orders should be verified before medication administration. Nurses should carefully review original medication orders before administration of the first dose and compare them with medications dispensed. Doses should not be administered unless the meaning of the original order is clear and unambiguous and there are no questions with respect to the correctness of the prescribed regimen. Nurses should check the identity and integrity (e.g., expiration date and general appearance) of the medications dispensed before administering them.

- Patients should inform appropriate direct health-care providers (e.g., physicians, nurses, and pharmacists) about all known symptoms, allergies, sensitivities, and current medication use. Patients should communicate their actual self-medication practices, even if they differ from the prescribed directions.

- Finally physicians should keep in mind that adverse drug reaction should be considered as an important differential diagnosis whereas it is usually hidden in other diagnosis (35). This is not attainable without taking a complete medical history especially a precise medication history. Unfortunately a drug-induced adverse event was diagnosed in the reported case after 4 months in this case.

Conclusion

Using handwritten prescription and inappropriate abbreviations, inadequate time for taking a brief medical history in pharmacy, lack of verifying name, dose and wrote before medication administration had roles to occur this multi-steps medication error in this case. Lack of considering adverse drug reaction as an important differential diagnosis caused to delay the patient problems and his disease therapy.

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