Overdose and intramuscular administration of Bacille Calmette-Guerin vaccine in a 2-month-old infant

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The Bacille Calmette-Guérin (BCG) vaccine is used against tuberculosis. According to the vaccination program in Turkey, DaBT-Hib-IPV (diphtheria-pertussis [acellular]-tetanus-haemophilus influenza type b-inactive polio vaccine), PVC13 (pneumoccocal conjugate vaccine) and BCG vaccines are given simultaneously to all 2-months-old infants, using different administration techniques. We report a 2-month-old infant who received an overdose and intramuscular BCG vaccine instead of DaBT-Hib-IPV. The patient was treated with isoniazid for six months and developed no complications during a one-year follow-up period.

Key words: infant, overdose and intramuscular BCG vaccine.

The Bacille Calmette-Guérin (BCG) vaccine has been used for 80 years against tuberculosis and is one of the most widely used of all current vaccines, reaching more than 80% of neonates and infants in countries where it is part of the national childhood immunization program. The World Health Organization (WHO) recommends that a single dose of BCG be given to neonates as soon as possible after birth in countries with a high prevalence of tuberculosis[1]. In Turkey, all 2-month-old infants are routinely vaccinated via the intradermal route with 0.05 ml BCG, in compliance with the national vaccination program of the Ministry of Health. Complications following BCG vaccination are rare, but vary greatly, and depend on the administration technique, the dose and the type of BCG preparation. There are few reports concerning BCG vaccine overdose or intramuscular administration; this report is unique in combining both subjects. We report a two-month-old-infant, intramuscularly vaccinated with a dosage of 1.0 ml BCG, 20 times higher than the standard 0.05 ml dose.

Case Report

A two-month-old full-term girl, birthweight 3900 was accidentally vaccinated intramuscularly with a dose of 1.0 ml BCG in her left musculus quadriceps femoris, in a local healthcare center. As soon as the nurse giving the vaccine realized the mistake, the infant was referred to the hospital; this took place within two hours. According to the vaccination program in Turkey, DaBT-Hib-IPV, BCG and PVC13 vaccines are given to all 2-month-old infants using different administration techniques (Table II). The nurse had thought the vaccine she was administering to be DaBT-Hib-IPV. In the physical examination, the infant was 5400 g. She revealed no induration, inguinal lymphadenopathy or any local reactions, nor did she have any systemic symptoms; there was only a small red mark at the injection site. The complete blood count, blood chemistry and CRP values were within normal ranges. The patient was followed for 6 days in the hospital; there were no adverse events or local/systemic reactions in the follow-up period. Isoniazid 10 mg/kg/day was started as prophylaxis, and the patient was discharged from the hospital. Ten days after discharge, the infant was called to the Pediatric Infectious Disease outpatient clinic for a follow-up visit. There was no lymphadenopathy, no hepatomegaly, no scar, no induration. The liver function tests were also normal. Monthly follow-up visits were

planned to continue for one year. A PPD test was performed at the fourth month; the induration was found to be 5 mm. Isoniazid prophylaxis was given for six months. There was no problem during the subsequent period.

Discussion

The dermis and epidermis of skin are rich in antigen-presenting cells; the delivery of vaccines to these layers may be more efficient, in that the intradermal route may induce protective immune responses with smaller amounts of vaccine antigen[2]. On the other hand, the intramuscular route optimizes the immunogenicity of the vaccine and minimizes adverse reactions at the injection site. Muscle has an abundant blood supply, so it is probably spared the harmful effects of substances injected into it. Another way to administer a vaccine is via the subcutaneous route. Adipose tissue has poor vascularity and also much poorer drainage channels, retains injected material for much longer and therefore is more susceptible to adverse effects. Injecting a vaccine into the subcutaneous fat may result in slow mobilization and processing of the antigen and can be a cause of failure in such vaccines as hepatitis B, rabies and influenza. Furthermore, subcutaneous injections can cause abscesses and granulomas[3].

The BCG vaccine has been used for routine vaccination against tuberculosis in more than 80% of the world's population. Local and systemic side effects, although rare (1%-2% of immunizations), are associated with BCG vaccine. Local adverse reactions, such as subcutaneous abscess and regional lymphadenopathy, generally are not serious, and are usually self-limiting. Other complications, such as osteitis and disseminated fatal infection, occur only rarely[4,5].

In Turkey it is recommended that all children receive BCG vaccination to prevent development of tuberculosis. The vaccine is injected intradermally into the left upper arm (deltoid region). The correct dose is 0.05 ml for children under 12 months of age, and 0.1 ml for individuals 12 months or older. The correct administration technique and dosage of the BCG vaccine are very important. Severe local and systemic complications can develop due to technical errors such as injection of an excessively high dose of the vaccine or incorrect administration of the vaccine solution. Puliyel et al. reported on 857 infants who were accidentally vaccinated intradermally with a percutaneous BCG preparation, receiving about five times the upper limit of the currently recommended intradermal dose of BCG, of whom 11% had adverse local reactions, in most cases axillary lymphadenopathy[5]. This complication rate is markedly higher than the reported rate of 5% for total adverse reactions (2.5% injection site abscess, 1.5% severe local reaction and 1% lymphadenitis) in an Australian study in which the correct dose of BCG was given[6]. In another report, 19 children aged 11 to 14 years who were intradermally administered a stronger, high-dose percutaneous vaccine had lesions larger than those of 13 patients administered the correct dose. Neither group needed additional treatment[7]. In these studies, the errors occurred because of the similar packaging and labeling of the intradermal and percutaneous BCG preparations; the authors recommended clear packaging and labeling of the two products[5,7].

Ritz et al[8]. reported reported a 14-year-old girl who was inadvertently immunized with an excessively large dose of BCG vaccine (1.0 ml instead of 0.1 ml). A subcutaneous fluctuant tender lump at the injection site developed; this was surgically excised within 12 hours of immunization, and she was treated with isoniazid and rifampicin for six weeks. The patient developed no complications other than

Table I. PPD Scoring

PPD Measurement**	
0-5 mm	Negative
6-9 mm	Indefinable, repeat the test after one week: 6-9 mm is negative; 10 mm or more is positive.
10 mm and more	Positive/Tuberculosis infection

** PPD Measurement Table is adapted from T.C. Sağlık Bakanlığı Temel Hizmetleri Genel Müdürlüğü, Genelge 2008/14.

Table II. Vaccination Schedule, Turkish Ministry of Health (07.02.2014)

	Birth	1st month	2nd month	4th month	6th month	12th month	18th month	24th month	Primary school 1st grade	Primary school 8th grade
Hep-B	I	II			III					
BCG			I							
DTaP-IPA-Hib			I	II	III		B			
CPV			I	II	III	B				
MMR						I			B	
DTaP-IPV									B	
OPV					I		II			
Td										B
Hep-A							I	II		
Varicella						I				

Hep B: hepatits B, BCG: Bacille Calmette Guerin, DTap: diphteria tetanus pertussis, IPU: inactivated polio virus, Hib: Haemoptilus influenzae tybe b, CPV: conjugated pneumococcal vacine MMR: measles mumps, rubella, OPA: oral polio vacine, Td: tetanus diphteria Hep A: hepatitis A

a minor surgical scar[8]. In 1962, at a BCG clinic in Cardiff, 10 children were accidentally administered a dose of BCG that was 12-15 times the normal dose (too concentrated but in an appropriate volume). Their ages were between 3 and 13 years old. None of the children had local abscesses or discharging sinuses, or lymphadenopathy. All children were treated with isoniazid for 60 days[9]. These studies indicated that isoniazid treatment is effective in preventing serious local adverse effects after BCG overdose [8,9].

Benamar et al[10]., evaluating spontaneous reports of misuse and overdoses over a 4-year period reported adverse effects due to inappropriate use of BCG vaccine. The most common event was misuse of BCG vaccine, and a large number of these events consisted of the injection of a BCG vaccine instead of a tuberculin test (Table I). The most common adverse effects were related to injection-site reactions. Systemic signs, such as asthenia, fever and lymphadenopathy, were seen in half of the cases[10].

The consequences of intramuscular injection of BCG vaccine have very seldom been described. Pasteur et al. reported the case of a healthy 30-year-old man, where inadvertent intramuscular injection of BCG vaccine into an already tuberculin-sensitive individual resulted in ulceration, discharge and deltoid muscle wasting. Isoniazid therapy for 4 weeks was commenced, and healing appeared to be hastened by antituberculous chemotherapy[11].

There is no consensus on the approach to be followed in an infant given an overdose of BCG vaccine by means of an inappropriate technique. Since in our case the patient who was inadvertently given an excessive dose (1 ml instead of 0.05 ml, 20 times higher than the standard) was an infant, we considered it would be better to give INH prophylaxis for six months. No adverse events, systemic reactions or lymphadenopathy were observed over the course of one year. The favorable outcome in our patient may suggest that antituberculosis treatment is an effective management for BCG overdose and intramuscular administration. However, we do not know for certain whether INH affected the outcome. In our case, the nurse supposed the BCG vaccine to be DaBT-Hib-IPV. However, these vaccines are two different preparations. The BCG vial contains 20 doses, and the vaccine must be used within eight hours once reconstituted, while the DaBT-Hib-IPV vaccine contains one dose. The colors and the packaging of these vaccines are different, but their dissolution methods are similar. Under the vaccination program in Turkey, all 2-month-old infants are vaccinated with both DaBT-Hib-IPV-PCV13 and BCG (Table II). The healthcare professionals who play the major role in their administration must be experienced and well-educated about the vaccination program, as well as the techniques

and the dosages, in order to ensure appropriate vaccination.

Medical errors have been defined as a major public health problem all over the world, and usually are underreported. The incidence of overdose and/or inappropriate administration of BCG vaccine is not precisely known. Information about the subsequent management of these cases and any adverse events should be reported to the pharmacovigilance department.

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