CASE REPORT

Hypersensitivity Reaction to Chlorobutanol-Preserved Thiamine

Major Regis Vaillancourt, Captain Roxanne A. Kearns and Commander Michael Buchholz

Adverse drug reactions are a common problem encountered by clinicians. Approximately 30 percent of all hospitalized medical patients experience at least one adverse drug reaction during their hospitalization.[1] This case report illustrates the importance of considering inactive ingredients as potential allergen.

CASE

Mr. J.C. is a 52 year old Caucasian man who was admitted to the National Defence Medical Centre with a diagnosis of alcohol withdrawal syndrome. He had a 26 year history of alcohol abuse with subsequent partial gastrectomy for adenocarcinoma. He required B12 replacement therapy for documented B12 deficiency of mixed etiology. He had been non-compliant with his vitamin B12 therapy for at least two months prior to admission. The patient had a known allergy to penicillin with local hives.

On admission, the patient received thiamine hydrochloride 100 mg (Sabex) I.M. daily for three days, multivitamins 1 tablet po daily, folic acid 5 mg po daily, and sucralfate 1 g po qid. His delirium tremens was managed with lorazepam IV or po. On day seven of hospitalization, the patient developed an urticarial erythematous rash predominantly affecting upper limbs and truncal region. Despite the use of diphenhydramine po and an elimination process excluding common foods, soap, bed linens, the medications except lorazepam, the patient persisted with new urticarial lesions. Dermatology consultation confirmed the diagnosis of delayed allergic reaction — the most probable etiology being thiamine injections.

The patient was discharged on the 23rd day with persistent urticaria. Discharge medications included cimetidine 300 mg po qid, hydroxyzine 25 mg po qam and 50 mg po qhs for three weeks, Moisturel(R) lotion prn, and diphenhydramine 50 mg po qhs for one week.

The clinical pharmacist involved in this case raised the possibility of the preservative, chlorobutanol utilized in the thiamine injection manufactured by Sabex as the etiological agent rather than thiamine.

Forty-five days after the onset of the reaction, when the patient's skin rash resolved, the intradermal skin test using thiamine with and without preservative (Sabex) was performed with the patient's informed consent. With immediate resuscitative equipment at hand in a controlled environment, the intradermal test was performed on the forearms. An erythematous pruritic 2 cm papule was formed on the volar surface with the thiamine and preservative mixture. No reaction was observed with the mixture which was preservative free.

DISCUSSION

Hypersensitivity with thiamine has been reported and typically present as an urticarial rash and pruritis. The intradermal test dose is a recommended procedure to rule out a sensitivity reaction to thiamine.[2] The clinical pharmacist recommended the intradermal test to determine the offending agent as chronic replacement therapy would be necessary.

Chlorobutanol is a preservative used in topical, ophthalmic, parenteral, and otic preparations.[3,4] Hypersensitivity reactions to chlorobutanol, when used as a preservative have been reported.[5-7] One other reaction followed the use of chlorobutanol-preserved heparin which

Major Regis Vaillancourt, CD B.Pharm. was Pharmacy Clinical Services Officer at the National Defence Medical Centre at the time of preparation of this case report. Currently Major Vaillancourt is the Commanding Officer of the Regional Medical Equipment Depot of Canadian Forces Base, Chilliwack, BC.
Captain Roxanne A. Kearns, B.S.P.M. was a Pharmacy Resident at the National Defence Medical Centre at the time of preparation of this case report. Currently Captain Kearns is an Assistant Head of Pharmacy at Canadian Forces Hospital, Halifax, NS.
Commander Michael Buchholz, CD, M.D., F.R.C.P. is the head of Internal Medicine at Canadian Forces Hospital, Halifax, N.S.
Address correspondence to: Major Regis Vaillancourt, Commanding Officer, Regional Medical Equipment Depot, Canadian Forces Base, Chilliwack, BC V0X 2E0.
Acknowledgements: The authors wish to thank Richard Wagner for his professional support.

presented as an erythematous skin rash. The hypersensitivity to chlorobutanol was confirmed by an intradermal test.[5] Chlorobutanol-preserved DDAVP(R) was also implicated in one rash.[6] Chlorobutanol has been reported to cause mild conjunctivitis following the immersion of gel lenses in a solution containing this preservative.[7]

The rash developed seven days after initial exposure. This is in a normal range for newly developed allergic response.[8] The half-life of chlorobutanol is approximately 10 to 13 days.[4] This explains why the patient was still symptomatic on discharge, 20 days after the last dose of chlorobutanol preserved thiamine.

It is important to note the possibility of cross-sensitivity of chlorobutanol with chloral hydrate.[9] Table I is the list of Canadian products that the patient should avoid because they contain chlorobutanol as a preservative.

This case illustrates the necessity of having a list of inactive ingredients of pharmaceuticals available. Clinicians should always include the preservative as a suspected allergen and consider rechallenge whenever possible.

Table I: List of Canadian Products which contain chlorobutanol[10]

Brand Name	Generic name formulation
AK-CHLOR	CHLORAMPHENICOL ophthalmic solution
BACIGUENT	BACITRACIN topical
AK-SULF	SULFACETAMIDE ophthalmic solution
BETAXIN	THIAMINE injection
CHLOROPTIC(R)	CHLORAMPHENICOL ophthalmic solution
CHLOROPTIC(R) S.O.P.	CHLORAMPHENICOL ophthalmic solution
DDAVP(R)	DESMOPRESSIN nasal solution
DELATESTRYL(R)	TESTOSTERONE injection
DELESTROGEN(R)	ESTRADIOL injection
DEMO-CINEOL(R)	CINEOL-GUAIACOL injection
DOPRAM(R)	DOXAPRAM injection
FLURESS(R)	FLUORESCEIN-BENOXINATE ophth. solution
ISUPREL(R)	ISOPROTERENOL solution for inhalation
LACRI-LUBE(R)	PETROLATUM-MINERAL OIL ophth. ointment
LACRIL(R)	METHYLCELLULOSE ophthalmic solution
NEO-CORTEF(R)	NEOMYCIN-HYDROCORTISONE ophth. sol.
NEO-PAUSE(R)	TESTOSTERONE injection
NOVOCAIN(R)	PROCAINE injection
OPHTHAINE(R)	PROPARACAINE ophthalmic solution
PHOSPHOLINE IODIDE(R)	ECHOTHIOPHATE IODIDE ophth. solution
PMS ARTIFICIAL TEARS	POLYVINYL ALCOHOL ophthalmic solution
PMS ARTIFICIAL TEARS XTRA	POLYVINYL ALCOHOL-POVIDONE ophth. sol.
PMS ESTRADIOL VALERATE	ESTRADIOL injection
PONTOCAINE(R)	TETRACAINE injection
PRESSYN(R)	VASOPRESSIN injection
RHINO-VACCIN	EPHEDRINE topical
ROBINUL(R)	GLYCOPYRROLATE injection
TEARS PLUS(TM)	POLYVINYL ALCOHOL-POVIDONE ophth. sol.
TOBREX(TM)	TOBRAMYCIN ophthalmic solution

REFERENCES

1. Jick H. Drugs-remarkably nontoxic. *New Engl J Med* 1974; 291:824.
2. American Society of Hospital Pharmacists, American Hospital Formulary Service 1990:2121.
3. Mackeen DL. The Pharmacist's role: Contact Lens Solutions. *Am Pharm* 1986; NS26:691-6.
4. Poisindex Editorial staff (Rumack BH and Spoerke DG eds.). Chloral Hydrate and related agents, Poisindex Information System, Micromedex Inc. Denver, Colorado, 1990.
5. Dux S, Pitlik S et al. Hypersensitivity reaction to chlorobutanol-preserved heparin. *Lancet* 1981; 1:149.
6. Itabashi A, Katayama S, Yamaji T. Hypersensitivity to chlorobutanol in DDAVP solution. *Lancet* 1982; 1:108.
7. Polak BCP. Drugs used in ocular treatment. In: Dukes MNG. Meyler's Side Effects of Drugs. Elsevier Science, Amsterdam; 1988:988-98.
8. Klaassen CD. Principles of toxicology. In: Gilman AG, Goodman LS, Rall TW, and Murad F eds. The pharmacologic basis of therapeutics. 7th edition. Toronto. Collier MacMillan Canada Inc. 1592-1604.
9. Drugdex Editorial staff (Gelman CR and Rumack BH eds). Topical medications — Cross sensitization with systemic medications. Drugdex Information system, Micromedex Inc. Denver, Colorado. 1990.
10. Association pharmaceutique canadienne, compendium des produits et specialités pharmaceutiques vingt-cinquième édition 1990.