The compatibility of tetrahydrozoline hydrochloride solutions

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THE PURPOSE of this communication is to present findings concerning the compatibility of the commercially available tetrahydrozoline hydrochloride (Tyzine) nasal and ophthalmic solutions (Visine eye drops) with other medicaments that are commonly used in the treatment of nasal and ophthalmic conditions. It is felt that this study will aid the pharmacist and the physician in the compounding and prescribing of extemporaneous prescriptions utilizing tetrahydrozoline solutions.

Tetrahydrozoline hydrochloride is a sympathomimetic amine designated chemically as 2-(1,2,3,4-tetrahydro-1-naphthyl)-imidazoline hydrochloride and having the empirical formula $C_{13}H_{17}N_2Cl$. When applied topically to the nasal mucosa, the drug causes vasoconstriction, which results in a reduction of local swelling and congestion.[1,2,3] It is administered in 0.1% and 0.05% concentrations and is also used as an ocular decongestant in concentrations of 0.05%.

Tetrahydrozoline hydrochloride is a water-soluble salt consisting of a racemic mixture of two isomers. It is a white crystalline solid having a melting point of 256–257°C. The pH of a 1% aqueous solution is approximately 6.2.

Experimental

Tetrahydrozoline hydrochloride nasal solution is a 0.1% isotonic, citrate buffered, yellow colored solution containing thimerosal as the preservative. The solution is at pH 5.5.

Tetrahydrozoline hydrochloride ophthalmic solution is a 0.05% clear, isotonic, borate buffered, sterile solution, containing thimerosal as the preservative. The solution is at pH 6.2–6.3.

Physical compatibility studies were made by combining a 0.1% tetrahydrozoline hydrochloride nasal solution or a 0.05% tetrahydrozoline hydrochloride ophthalmic solution with the additive under test in the concentration commonly employed. Observations in physical appearance were made initially and after storage for 1, 3, 7, and 30 days at 25°C. The results are shown in Tables I and II.

The chemical stability of tetrahydrozoline hydrochloride nasal solution was also studied in combination with se-

Table I—Physical Compatibility of Tetrahydrozoline Hydrochloride Nasal Solution after One Month

Additive	Concentration	Remarks
Antibiotics		
Sodium Penicillin G	10,000 u./cc.	clear
Dihydrostreptomycin Sulfate	50 mg./cc.	clear
Oxytetracycline HCl	5 mg./cc.	clear, residue after 3 days
Chlortetracycline HCl	5 mg./cc.	clear, residue after 3 days
Polymyxin B Sulfate	500 u./cc.	clear
Bacitracin	500 u./cc.	clear
Neomycin Sulfate	1.0 mg./cc.	clear
Tyrothricin	0.2 mg./cc.	precipitate formed
Antiseptics		
Cetyldimethylbenzyl Ammonium Chloride	1/50,000	cloudy, precipitate forms slowly
Cetylpyridinium Chloride	1/50,000	cloudy, precipitate forms slowly
Benzalkonium Chloride	1/50,000	cloudy, precipitate forms slowly
Hormones		
Prednisolone	0.2 mg./cc.	clear
Prednisone	0.2 mg./cc.	clear
Hydrocortisone	0.2 mg./cc.	clear
Local Anesthetics		
Procaine HCl	1%	clear
Benzyl Alcohol	3%	clear
Butacaine Sulfate	1%	clear, residue after few hrs.
Cocaine HCl	3%	clear
Tetracaine HCl	2%	clear, crystals formed after 2 weeks
Antihistamines		
Chlorpheneramine Maleate	5 mg./cc.	clear
Pyrilamine Maleate	5 mg./cc.	clear
Others		
D-amphetamine Sulfate	10 mg./cc.	clear
Hydroxyzine HCl	5 mg./cc.	clear
Ephedrine Sulfate	5 mg./cc.	clear
Chlorobutanol	0.5 %	clear
Silver Nitrate	0.5 %	precipitate formed
Mild Silver Protein	10–20%	readily dispersible, residue formed after one month
Strong Silver Protein	1 %	not soluble
Boric Acid	2 %	clear
Ascorbic Acid	1 %	clear, color change
Camphor	0.05%	clear
Menthol	0.05%	clear

* Received from the Pharmaceutical Research and Development Department, Chas. Pfizer & Co., Inc.

[1] *New and Nonofficial Drugs*, J. B. Lippincott Co., Philadelphia, 1958, p. 213.

[2] Menger, H. C., *N.Y. State J. Med.*, **55**, 812 (1955).

[3] Parish, F. A., *Med. Times*, **82**, 917 (1954).

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TABLE II—Physical Compatibility of Tetrahydrozoline Hydrochloride Ophthalmic Solution After One Month

Additive	Concentration	Remarks
Antibiotics		
Sodium Penicillin G	10,000 u./cc.	clear
Dihydrostreptomycin Sulfate	50 mg./cc.	clear
Oxytetracycline Hydrochloride	5 mg./cc.	clear, residue after 3 days
Chlortetracycline Hydrochloride	5 mg./cc.	clear, residue after 3 days
Polymyxin B Sulfate	500 u./cc.	clear
Bacitracin	500 u./cc.	clear
Neomycin Sulfate	1 mg./cc.	clear
Antiseptics, caustics		
Benzalkonium Chloride	1/50,000	clear
Cetylpyridinium Chloride	1/50,000	clear
Silver Nitrate	0.5%	precipitate formed
Mild Silver Protein	10%	readily dispersible
Strong Silver Protein	1 %	not readily dispersible, precipitate formed
Mercuric Chloride	1/50,000	clear
Zinc Sulfate	1 %	clear
Hormones		
Prednisolone	0.2 mg./cc.	clear
Prednisone	0.2 mg./cc.	clear
Hydrocortisone	0.2 mg./cc.	clear
Local Anesthetics		
Procaine Hydrochloride	1%	clear
Cocaine Hydrochloride	2%	clear
Butyn Sulfate	2%	clear, residue formed after 2 days
Mydriatics		
Atropine Sulfate	0.05%–1%	clear
Homatropine Hydrobromide	0.05%–1%	clear
Miotics		
Pilocarpine	0.05%–1%	clear
Others		
Chlorobutanol	0.5%	clear
Methocel 4000 cps.	0.5%	clear

lected ingredients. A spectrophotometric assay method was employed. These samples were assayed initially and after 3 weeks' storage at 50°C. The results are tabulated in Table III.

Discussion of Results

As can be seen from Tables I and II, tetrahydrozoline hydrochloride solutions are generally compatible, physically, with most of the substances tested.

Tetrahydrozoline hydrochloride has, as would be expected, the incompatibilities of chlorides. This is shown by its reaction with silver compounds.

Cationic surface active agents are contraindicated for use in tetrahydrozoline nasal solution since the yellow dye that is present is precipitated. Tyrothricin also precipitates this dye. This is not true in the case of tetrahydrozoline ophthalmic solution since there is no dye present to react.

Antibiotics such as the tetracyclines and the penicillins usually have a shelf-life for a period of 2 to 3 days in aqueous solution under refrigerated conditions. After this period, in the case of the tetracyclines, a darkening and a residue appear. When combined with tetrahydrozoline solutions there is no evidence of acceleration of this normal decomposition and, therefore, these solutions are compatible for the period of 2 to 3 days.

The data presented in Table III indicates the extreme chemical stability of tetrahydrozoline hydrochloride, under accelerated conditions, with various additives such as corticoids, antihistamines and antibiotics.

When adding other ingredients to tetrahydrozoline hydrochloride ophthalmic solution aseptic techniques should be employed since the solution is sterile and the introduction of contaminants is to be avoided. ■

TABLE III—Chemical Stability of Tetrahydrozoline Hydrochloride Nasal Solution After 3 Weeks at 50°

Additive	Concentration	Tetrahydrozoline Hydrochloride Potency After 3 Weeks[a]
Prednisolone	0.2 mg./cc.	0.99 mg./cc.
Hydrocortisone	0.2 mg./cc.	1.0 mg./cc.
Neomycin	0.6 mg./cc.	1.0 mg./cc.
Penicillin G Potassium	10,000 u./cc.	1.1 mg./cc.
Sulfanilamide	20 mg./cc.	1.1 mg./cc.
Sulfathiazole	50 mg./cc.	1.0 mg./cc.
Procaine Hydrochloride	10 mg./cc.	1.0 mg./cc.
Polymyxin B. Sulfate	500 u./cc.	1.0 mg./cc.
Pyrilamine Maleate	5 mg./cc.	1.0 mg./cc.
Chlorpheneramine Maleate	5 mg./cc.	1.0 mg./cc.

[a] Initial Assay 1.0 mg./cc.