

Visual Compatibility of Various Injectable Neuroleptic Agents with Benztropine and Lorazepam in Polypropylene Syringes

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ABSTRACT

Background: The nursing staff at the authors' hospital are frequently called upon to administer medications by intramuscular injection during psychiatric emergencies. Many of these medications are considered incompatible when mixed together, and up to 3 separate injections may be required for a single patient. The need for multiple injections increases the risk of needle-stick injury in these situations.

Objectives: The visual compatibility of various combinations of haloperidol, loxapine, chlorpromazine, benztropine, and lorazepam was studied, with the aim of reducing the number of injections required and hence reducing the risk to staff and increasing patient comfort.

Methods: To emulate the setting of a nursing unit, single syringes of selected combinations of medications were prepared on a clean tabletop under fluorescent light at room temperature. The syringes were visually inspected for haze, immiscibility, precipitation, and colour change at 15, 30, and 45 min and at 1, 2, 3, and 4 h after mixing.

Results: The haloperidol-benztropine mixtures and the haloperidol-benztropine-lorazepam mixtures were compatible on visual inspection throughout the observation period. The loxapine-benztropine and loxapine-lorazepam mixtures showed immediate incompatibility, as did the chlorpromazine-lorazepam and benztropine-lorazepam mixtures. A table of compatibilities was produced for quick reference on nursing units.

Conclusions: Mixtures of haloperidol and benztropine and of haloperidol, benztropine, and lorazepam are compatible for periods of up to 4 h. The combinations of loxapine and benztropine, loxapine and lorazepam, chlorpromazine and lorazepam, and benztropine and lorazepam should not be mixed before administration.

Key words: haloperidol, loxapine, chlorpromazine, benztropine, lorazepam, visual compatibility, needle-stick injury

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RÉSUMÉ

Historique : Le personnel infirmier de l'hôpital où sont rattachés les auteurs est souvent sollicité à administrer des médicaments par voie intramusculaire au cours d'urgences psychiatriques. Beaucoup de ces médicaments sont jugés incompatibles lorsqu'on les mélange; par conséquent jusqu'à trois injections séparées pour un même patient peuvent être nécessaires pour les administrer. Or les nombreuses injections accroissent le risque de blessure avec aiguille dans ces situations.

Objectifs : La compatibilité visuelle des diverses associations d'halopéridol, de loxapine, de chlorpromazine, de lorazépam et de benztropine a été étudiée dans le but de réduire le nombre d'injections nécessaires et partant de diminuer le risque pour le personnel et d'améliorer le confort du patient.

Méthodes : Afin de reproduire l'environnement d'une unité de soins, des seringues uniques d'associations médicamenteuses choisies ont été préparées sur un comptoir stérile sous éclairage fluorescent, à température ambiante. Les seringues ont été inspectées visuellement pour déceler toute turbidité, immiscibilité, précipitation ou altération de la couleur 15, 30 et 45 minutes, puis 1, 2, 3 et 4 heures après avoir mélangé les médicaments.

Résultats : L'association halopéridol-benztropine et halopéridol-benztropine-lorazépam étaient compatibles à l'inspection visuelle pendant toute la durée de l'étude. L'association loxapine-benztropine et loxapine-lorazépam ont immédiatement montré une incompatibilité, tout comme les associations chlorpromazine-lorazépam et benztropine-lorazépam. Un tableau des compatibilités a été élaboré comme aide-mémoire sur les unités de soins.

Conclusions : Les associations halopéridol-benztropine et les associations halopéridol-benztropine-lorazépam sont compatibles pendant un maximum de quatre heures. Les associations loxapine-benztropine, loxapine-lorazépam, chlorpromazine-lorazépam, et benztropine-lorazépam ne devraient pas être préparées avant leur administration.

Mots clés : halopéridol, loxapine, chlorpromazine, benztropine, lorazépam, compatibilité visuelle, blessure avec aiguille

INTRODUCTION

Neuroleptics such as haloperidol, loxapine, and chlorpromazine are commonly administered to acutely agitated patients in the emergency department and on the psychiatric ward, when patients are uncooperative with treatment and refusing to take medications orally. Because neuroleptics may cause extrapyramidal symptoms, an anticholinergic such as benztropine is often given concurrently to prevent these symptoms. In addition, many patients benefit from a sedating anxiolytic such as lorazepam. Unfortunately, some combinations of these medications are considered incompatible, so the drugs must be injected separately. From the patient's perspective, a single injection would be more comfortable. For staff, any engineering controls that can be implemented to reduce needle-stick injury would be valuable.

A literature search of the MEDLINE database was done for the period from 1966 onward with the key words *haloperidol*, *loxapine*, *chlorpromazine*, *benztropine*, *lorazepam*, *compatibility*, *miscibility*, and *immiscibility*. However, relatively little literature exists regarding the compatibility of neuroleptics with benztropine and lorazepam, either in standard reference texts¹ or original research articles. This study was conducted to determine the visual compatibility of the injectable neuroleptics haloperidol, loxapine, and chlorpromazine with the anticholinergic benztropine and the anxiolytic lorazepam in polypropylene syringes.

METHODS

Specified volumes of haloperidol, loxapine, or chlorpromazine were drawn up into polypropylene syringes (Becton-Dickinson & Co., Franklin Lakes, New Jersey); benztropine, lorazepam, or both were subsequently drawn up into the syringes (see Table 1). The drug solutions were not drawn into the syringe in any particular order. The syringe contents were gently swirled for 15 s to ensure complete mixing, and each syringe was then sealed with a capped needle. The syringe contents were not swirled again during the study period. One syringe was prepared for each combination. The procedure was performed on a clean tabletop, in a manner that minimized bubbles and foaming. The concentrations of the neuroleptics tested were haloperidol 5 mg/mL (Sabex), loxapine HCl 50 mg/mL (Wyeth-Ayerst), and chlorpromazine 25 mg/mL (Sabex). Benztropine mesylate 1 mg/mL (MSD) and lorazepam 4 mg/mL (Wyeth-Ayerst) were the anticholinergic and anxiolytic agents, respectively. A total of 18 different combinations were prepared (Table 1).

Each syringe was examined visually with a magnifying glass against both a black and a white background, to check for haze, immiscibility, precipitation, or colour change. Observations were made immediately after preparation of each syringe and at 15, 30, and 45 min and 1, 2, 3, and 4 h afterward. The syringes were kept under constant exposure to fluorescent light at room temperature (20°C).

Table 1. Combinations of Neuroleptic, Anticholinergic, and Anxiolytic Agents Prepared and Observed for Visual Compatibility*

Syringe	Haloperidol	Loxapine	Chlorpromazine	Benztropine	Lorazepam	Compatibility
1	10 mg (2 mL)	–	–	2 mg (2 mL)	–	Compatible
2	10 mg (2 mL)	–	–	1 mg (1 mL)	–	Compatible
3	5 mg (1 mL)	–	–	2 mg (2 mL)	–	Compatible
4	10 mg (2 mL)	–	–	2 mg (2 mL)	2 mg (0.5 mL)	Compatible†
5	5 mg (1 mL)	–	–	1 mg (1 mL)	2 mg (0.5 mL)	Compatible†
6	–	50 mg (1 mL)	–	2 mg (2 mL)	–	Incompatible‡
7	–	25 mg (0.5 mL)	–	2 mg (2 mL)	–	Incompatible‡
8	–	50 mg (1 mL)	–	1 mg (1 mL)	–	Incompatible‡
9	–	50 mg (1 mL)	–	2 mg (2 mL)	2 mg (0.5 mL)	Incompatible§
10	–	25 mg (0.5 mL)	–	2 mg (2 mL)	2 mg (0.5 mL)	Incompatible§
11	–	50 mg (1 mL)	–	–	2 mg (0.5 mL)	Incompatible¶§
12	–	25 mg (0.5 mL)	–	–	2 mg (0.5 mL)	Incompatible¶
13	–	12.5 mg (0.25 mL)	–	–	2 mg (0.5 mL)	Incompatible¶
14	–	–	100 mg (4 mL)	–	2 mg (0.5 mL)	Incompatible§
15	–	–	50 mg (2 mL)	–	2 mg (0.5 mL)	Incompatible§
16	–	–	50 mg (2 mL)	2 mg (2 mL)	2 mg (0.5 mL)	Incompatible§
17	–	–	–	2 mg (2 mL)	2 mg (0.5 mL)	Incompatible
18	–	–	–	1 mg (1 mL)	2 mg (0.5 mL)	Incompatible

*Entries are given as quantity and volume of drug.

†Solution appeared to be immiscible initially but became miscible with gentle mixing.

‡Solution appeared to be immiscible initially and remained immiscible for 1 h before developing a clear appearance.

§Solution turned yellow.

¶The time to appearance of precipitate was related to the amount of loxapine in the syringe and the total volume of the mixture.

RESULTS

The results are summarized in Table 1. All haloperidol-benztrapine combinations were visually compatible at all observation times. No haze, precipitate, or immiscibility was observed with these combinations. Syringes containing haloperidol, benztrapine, and lorazepam showed some immiscibility on initial mixing, but this cleared with gentle shaking. Immiscibility was characterized by *schlieren* lines, which were oily or greasy in appearance. *Schlieren* lines (from the German word for streaks or striations) are often seen with variations in density during fluid dynamic studies of chemical mixing or gas flow. The contents of these syringes appeared compatible at all subsequent observation times. The syringes containing loxapine and benztrapine showed immiscibility on mixing and until the 1-h observation point, after which the solution remained clear until the last observation point, at 4 h. Syringes with loxapine, benztrapine, and lorazepam were initially immiscible and cleared with shaking, but had yellowed by the 30-min observation point. Syringes containing loxapine and lorazepam were immiscible on mixing and did not clear with shaking. Precipitate formed within 15 min in the syringe with loxapine 25 mg and lorazepam 2 mg and within 45 min in the syringe with loxapine 12.5 mg and lorazepam 2 mg, demonstrating obvious incompatibility. The loxapine 50 mg and lorazepam 2 mg combination turned yellow within 30 min, and a precipitate had formed by 3 h. Syringes with chlorpromazine and lorazepam combinations showed immiscibility that did not clear with shaking, and these mixtures turned yellow within 45 min. The syringe with chlorpromazine, benztrapine, and lorazepam was similar in appearance, with yellowing observed at the 15-min observation point. The benztrapine-lorazepam combinations showed immiscibility that did not clear with initial shaking. The syringe with benztrapine 2 mg and lorazepam 2 mg eventually cleared (at 45 min), whereas the one with benztrapine 1 mg and lorazepam 2 mg had cleared by the 3-h observation point.

DISCUSSION

In 1999 at Richmond Hospital, a total of 1610 code white situations (management of aggressive behaviour) occurred, including 1457 cases stand-by situations on the psychiatric unit. In approximately 70% of these situations, chemical restraints were administered. Staff at the hospital are examining ways to minimize the risk of needle-stick injury in these situations.

Haloperidol-benztrapine is perhaps the most frequently prescribed combination for acute psychosis,

and the ability to administer these medications with a single injection would be welcomed by nursing staff. Somewhat unexpectedly, the syringes containing both haloperidol and benztrapine were visually compatible at all observation times. This finding contrasts with previously published studies on this combination.^{2,3} One article reported a white precipitate forming within 5 min in all syringes containing haloperidol and various anticholinergic agents, including benztrapine, and the precipitate worsened with swirling.² In a previous study of low-dose haloperidol combined with benztrapine, most of the combinations tested also precipitated.⁴ Haloperidol has been previously reported as visually compatible with lorazepam¹; therefore, this combination was not assessed during this study. In addition, the triple-combination syringes with haloperidol, benztrapine, and loxapine showed some immiscibility initially, but the mixtures cleared after gentle shaking and remained clear over the next 4 h. Haldol (haloperidol 5 mg/mL; McNeil) had been discontinued from the Canadian market at the time of the study, and therefore could not be assessed. It is possible that the compatibility of Haldol may differ from that of the Sabex product used here and any other available generic brands of haloperidol. The American formulation of Haldol contains haloperidol lactate and lactic acid for pH adjustment, whereas the Sabex formulation contains haloperidol base and lactic acid for pH adjustment. These differences in formulation may explain the differences in compatibility between this and previous studies. The Canadian formulation of benztrapine (as the mesylate) used in this study is identical with the American benztrapine formulation.

The combined volume of the mixture of haloperidol 10 mg, benztrapine 2 mg, and lorazepam 2 mg was 4.5 mL. An excellent recent review article on intramuscular injection technique⁵ has stated that injection into a large muscle group should not exceed 5 mL in adults, with 2.5 mL into the ventrogluteal injection site, 4 mL into the dorsogluteal site, and 5 mL into the vastus lateralis (outer thigh) being safe for injection. Obviously, due judgement by the nurse administering the injection as to the maximal tolerable volume for each patient is required, and acceptable volumes are probably lower for elderly patients and those with decreased muscle mass.

At the authors' institution, loxapine is increasingly used for treatment of psychiatric emergencies and may be a "first choice" drug in the elderly population, because it is associated with fewer adverse effects, including extrapyramidal symptoms, than haloperidol.⁶ Loxapine is not listed in a widely accepted reference text on the compatibility of parenteral medications,¹ and compatibility information is scarce. The observations



reported here indicate that loxapine should not be combined in the same syringe with benztropine, lorazepam, or both: definite precipitation occurred when loxapine was combined with lorazepam, and immiscibility and early yellowing of solutions occurred when it was mixed with benztropine.

Loxapine, which contains the cosolvent polypropylene glycol, was incompatible in all of the combinations tested in this study. Lorazepam, which contains polyethylene glycol and propylene glycol, showed incompatibility with loxapine, chlorpromazine, and benztropine. The solvents mentioned are often used when a drug is poorly soluble in water. When products containing polyethylene glycol or propylene glycol are mixed with water from another product, a precipitate often forms.

Chlorpromazine has been previously shown to be compatible with benztropine in syringes,¹ so this combination was not tested again. As with loxapine, chlorpromazine showed incompatibility with lorazepam, and this combination should be avoided.

The benztropine-lorazepam combination was studied on the basis that if a 3-drug combination of neuroleptic, benztropine, and lorazepam was incompatible because of the neuroleptic, the number of injections needed could still be reduced if benztropine and lorazepam were compatible. Unfortunately, immiscibility occurring with this combination did not clear immediately despite shaking and only cleared after an extended period of time (45 min to 3 h), which indicates that use of this combination is inadvisable. This conclusion is somewhat paradoxical, since both of the syringes containing haloperidol, benztropine, and lorazepam remained visually compatible throughout the observation period. It is possible that the dilutional effects of the extra volume (1 to 2 mL) resulting from the addition of haloperidol facilitated compatibility.

To mimic usual conditions in the emergency department or on the nursing unit, this study was conducted on a tabletop and not in a laminar air flow hood. The syringes were kept under constant exposure to fluorescent light at room temperature. These results are believed to be valid, since these conditions follow common practice on nursing units. Other studies of physical compatibility of haloperidol and benztropine medications have been conducted in a laminar air flow hood. It is unlikely that this affected the results.

In this study, only visual compatibility was assessed. Chemical stability and potency of the individual agents after mixing with other drugs were not evaluated. It is possible that a chemical incompatibility not manifested by a change in visual appearance occurred with

these medication combinations. In addition, since polypropylene syringes are not completely clear, it is possible that very fine visual changes indicating incompatibility, such as opalescence, occurred but were not detected.

In summary, haloperidol-benztropine and haloperidol-benztropine-lorazepam in common dosage combinations were visually compatible for up to 4 h when mixed in syringes. Loxapine was visually incompatible when mixed with either benztropine or lorazepam in commonly prescribed dosages. Chlorpromazine was visually incompatible with lorazepam when mixed in commonly prescribed dosages. The combination of benztropine and lorazepam showed clearing only after an extended period of time; it should therefore be considered visually incompatible and should be avoided. This compatibility information will be beneficial to staff who must administer intramuscular injections during psychiatric emergencies. A table of compatibilities has been produced and is now in use for quick reference on nursing units at the authors' hospital.

References

1. Trissel L. *Handbook on injectable drugs*. 11th ed. Bethesda (MD): American Society of Health-System Pharmacists; 2001.
2. Gibler B, Kim MS, Raleigh F. Visual compatibility of neuroleptics with anticholinergics or antihistamines in polyethylene syringes. *Am J Hosp Pharm* 1994;51:27091-.
3. Raleigh F, Gibler B. Haldol-benztropine incompatibility [letter]. *Hosp Pharm* 1994;29:76.
4. Jackson CW, Cunningham K. Compatibility of haloperidol lactate with benztropine mesylate. *Am J Hosp Pharm* 1994;51:2962-3.
5. Rodger MA, King L. Drawing up and administering intramuscular injections: a review of the literature. *J Adv Nursing* 2000;31: 574-82.
6. Carlyle W, Ancill RJ, Sheldon L. Aggression in the demented patient: a double-blind study of loxapine versus haloperidol. *Int Clin Psychopharmacol* 1993;8:103-8.

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