ELSEVIER

Il Farmaco 57 (2002) 925–930

IL FARMACO

www.elsevier.com/locate/farmac

Physicochemical compatibility between thiocolchicoside injections (Miotens®) and pharmaceutical products frequently used for combined therapy

Roberto Anacardio [a], Orietta Perilli [a], Federica Pagnanelli [a], Sandro Bartolini [a], Marco M. Gentile [a], Pietro Mazzeo [b], Giuseppe Carlucci [c,*]

[a] *Research & Development, L'Aquila Research Centre, Dompé SpA, via Campo di Pile, 67100 L'Aquila, Italy*
[b] *Dipartimento di Chimica, Ingegneria Chimica e Materiali, Università di L'Aquila, via Vetoio, 67100 L'Aquila, Italy*
[c] *Dipartimento di Scienze del Farmaco, Facoltà di Farmacia, Università 'G. D'Annunzio' Chieti, via dei Vestini, 66013 Chieti, Italy*

Received 9 March 2002; accepted 1 June 2002

Abstract

Thiocolchicoside (Miotens®), a muscle relaxant agent, is frequently administered in association regimen with other drugs, such as anti-inflammatory drugs or vitamins. The aim of this study was to investigate the physicochemical compatibility between thiocolchicoside (Miotens®) and other injectable drugs frequently used in association. Physicochemical properties of thiocolchicoside mixtures with different drugs, including colour, clarity, pH and drug content were observed or measured before and after (3 h) mixing at room temperature. Results show that the association of Miotens® with different anti-inflammatory drugs and vitamins does not cause, up to 3 h from mixing, any significant variation in the physicochemical parameters mentioned above. In conclusion the results obtained demonstrated the physicochemical compatibility of thiocolchicoside (Miotens®) with diverse anti-inflammatory drugs and vitamins.

Keywords: Thiocolchicoside; Pharmaceutical analysis; HPLC; Drugs interaction

1. Introduction

Thiocolchicoside, a sulfur derivative of colchicine, is prescribed for the treatment of traumatic, orthopaedic and rheumatic disorders due to its muscle relaxant, anti-inflammatory and analgesic properties [1]. Since it is very often co-administered by the intramuscular route with other drugs, the possible interactions between the drugs used must be carefully evaluated. The combined therapy requires the knowledge of the mixture physicochemical compatibility, which can be achieved by determining the possible variations of the main physicochemical parameters, such as appearance (physical state), pH and content of all active drugs of the mixture. Two mixed pharmaceutical products can be considered compatible when no significant variation of the physicochemical parameters of the mixture occurs. In fact, when two or more substances are mixed together, physical changes can occur, such as phase separation, formation of oil droplets and crystals [2]. Chemical incompatibility can take place with a variation of pH or, in extreme conditions, with a decrease in the drug content. The results of these modifications can cause a variation of therapeutic properties and undesirable side effects. Generally drugs in an extemporary mixture are considered chemically incompatible when the content decrease of active drugs is more than 10% of their nominal value [3–5].

When the incompatibilities result in visible changes such as precipitation, turbidity or haziness, changes in colour or viscosity, effervescence, or formation of immiscible liquid layers, the term physical incompatibility or, more accurately, visual incompatibility is

* Corresponding author
E-mail address: g.carlucci@unich.it (G. Carlucci).

0014-827X/02/$ - see front matter
PII: S0014-827X(02)01284-3

used. When interactions between drugs result in molecular changes or rearrangements to different chemical entities of the active compounds, the term chemical incompatibility is used. Drugs may undergo a variety of chemical degradation pathways, such as hydrolysis, oxidation or reduction reactions, photodegradation, racemization or epimerization. The most important factors that influence the rate of drugs decomposition in drug delivery systems are solution pH and temperature. Drug concentration, light exposure and solution ion strength are also important factors. Most chemical incompatibilities are not visibly observable, therefore a useful technique to assure the drugs pharmaceutical integrity is to perform the quantitative determination of the drugs before and after mixing by means of very selective and sensitive analytical methods such as the chromatography.

In this study an experimental protocol was designed to investigate the physicochemical compatibility of the associations between Miotens® injection, a new thiocolchicoside parenteral drug formulation, and the following anti-inflammatory drugs and vitamins marketed products: Orudis® Soluzione i.m. (Rhône-Poulenc-Rorer), Artrosilene® Fiale (Dompé Farmaceutici), Voltaren® Fiale (Geigy), Feldene® Fiale (Pfizer), Bentelan® 4 mg/2 ml Soluzione Iniettabile (Sigma-Tau), Rexalgan® (Dompé Farmaceutici), Tora-dol® 30 (Recordati), Dobetin® 5000 (Angelini), Aspegic® 1000 Iniettabile (Sanofi-Synthelabo), Mionevrasi® i.m. (Roche). The following physicochemical parameters were evaluated immediately after mixing and after 1 and 3 h at room temperature: colour, clarity, pH and drugs content.

The results obtained demonstrated the physicochemical compatibility of Thiocolchicoside (Miotens®) with diverse anti-inflammatory drugs and vitamins.

2. Experimental

2.1. Chemicals

Acetonitrile (HPLC grade) and disodium hydrogenphosphate (AnalaR grade) were supplied by Fluka Chemika-BioChemika (Buchs, Switzerland). Water (HPLC grade) was obtained by passage through the ELIX 3 and Milli-O Academic water purification system (Millipore, Bedford, MA, USA). Diclofenac sodium salt, acetylsalicylic acid, piroxicam, ketorolac, ketoprofen, betamethasone 21-phosphate sodium salt, cocarboxilase, pyridoxine and cyanocobalamin were purchased from Sigma–Aldrich (Milan, Italy) and used for the chromatographic identification of the active principles. Thiocolchicosideand ketoprofen lysine salts were supplied by Pharmacy Laboratory Dompé. Other chemicals and reagents were of analytical grade.

The following marketed products were used in the mixture preparation: Miotens® injection: thiocolchicoside 4 mg, NaCl 10.1 mg, sodium monobasic phosphate monohydrated 5.5 mg, sodium dibasic phosphate decahydrated 33.4 mg, water for injection; Artrosilene® Fiale: ketoprofen lysine salt 160 mg, citric acid, NaOH, water for injection; Orudis® Soluzione i.m.: ketoprofen 100 mg, arginine, citric acid monohydrate, benzyl alchol, water for injection; Voltaren® Fiale: sodium diclofenac 75 mg, mannytole 18 mg, sodium metabisulfite 2 mg, benzyl alcohol 120 mg, propylene glycol 600 mg, NaOH, water for injection; Feldene® Fiale: piroxicam 20 mg, sodium phosphate monobasic monohydrate 2.5 mg, nicotinamide 30 mg, propylene glycol 400 mg, EtOH 100 mg, benzyl alcohol 20 mg, NaOH 4.8 mg, concd. HCl 4.3 mg, water for injection; Tora-dol® 30: ketorolac trometamine 30 mg, alcohol 100 mg, NaCl 4.35 mg, water for injection; Rexalgan®: tenoxicam 20 mg, mannite, NaOH, tromethamol, ascorbic acid, sodium EDTA; solvent ampoule: water for injection; Aspegic® 1000: lysine acetylsalicylate 1800 mg (equivalent to 1000 mg of acetylsalicylic acid), glycine; solvent ampoule: water for injection; Mionevrasi® i.m.: cyanocobalamin (vit. B_{12}) 1 mg, pyridoxine hydrochloride (vit. B_6) 100 mg, cocarboxilase (vit. B_1) 38.20 mg, aminoacetic acid; solvent ampoule: lidocaine hydrochloride 10 mg, water for injection; Bentelan® 4 mg/2 ml Soluzione Iniettabile: betamethasone disodium phosphate 5.263 mg (equivalent to 4 mg of betamethasone), phenol, NaCl, sodium metabisulfite, sodium EDTA, water for injection; Dobetin® 5000: cyanocobalamin 5000 μg, sodium acetate trihydrate, AcOH, water for injection.

2.2. Chromatographic system and conditions

HPLC analysis was carried out using a chromatographic system equipped with: a Model 717 autosampler, a Model 2690 pump, a Model 2487 UV–Vis detector (Waters, Milford, MA, USA). A Model 7725i sample injector (Rheodyne, Cotati, CA, USA) equipped with a 20 μl loop was used. Chromatographic data management was automated using a software Millennium[32] (Waters, Milford, MA, USA). The analysis was performed on an analytical (250×4.6 mm i.d.) Luna C_{18} (5 μm particle size) column (Phenomenex, CA, USA). Separations were performed at room temperature. Mobile phases, volumes injected and wavelengths used for the separation of several drug associations, together with typical retention times, are reported in Table 1. The mobile phase was prepared daily and delivered at a flow-rate of 1.0 ml min^{-1}. The chosen chromatographic conditions were suitable to get a good resolution between the active drugs of the mixture, as shown in Table 1.

Table 1
Chromatographic conditions

Mixture	Mobile phase Na_2HPO_4 0.05 M (pH 7.0)/CH_3CN	UV–Vis detection (nm)	Injected volume (μl)	Active molecule	Retention time (min)
Miotens®, Orudis®	65/35	282	6	thiocolchicoside ketoprofen	3.2 4.7
Miotens®, Artrosilene®	65/35	282	6	thiocolchicoside	3.2
				ketoprofen lysine salt	4.4
Miotens®, Voltaren®	65/35	282	8	thiocolchicoside diclofenac	3.3 10.1
Miotens®, Feldene®	65/35	365	8	thiocolchicoside piroxicam	3.3 4.6
Miotens®, Rexalgan®	65/35	365	8	thiocolchicoside tenoxicam	3.3 4.5
Miotens®, Bentelan®	75/25	282	20	thiocolchicoside betamethasone	7.5 17.6
Miotens®, Tora-dol®	75/25	254	10	thiocolchicoside ketorolac	4.4 6.2
Miotens®, Aspegic®	75/25	254	8	thiocolchicoside acetylsalicylic acid, lysine salt	4.8 3.0
Miotens®, Dobetin®	80/20	254	10	thiocolchicoside cianocobalamine	10.5 3.7
Miotens®, Mionevrasi®	80/20	254	10	thiocolchicoside	10.4
				vit. B_1 vit. B_6 vit. B_{12}	2.5 2.9 3.7

2.3. Sample preparation

The content of a single ampoule of Miotens® injection and one ampoule of each associated formulation were mixed in a 10 ml glass tube and maintained stopped at room natural light and temperature. Lyophilised powder formulations were previously dissolved in the solvent enclosed in the marketed product and then mixed with thiocolchicoside preparation. Before submitting for HPLC analysis, samples were diluted 10-fold with Milli-Q water.

2.4. Colour and pH

The colour and clarity of the mixtures were evaluated by visual examination of the solution against a white background. The pH was measured by a Model PHM 92 pHmeter (Radiometer, Copenhagen). These parameters were evaluated before mixing, for each single formulation, and at time 0 and after 1 and 3 h of mixing for the mixtures.

3. Results and discussion

The features of the preparations selected for the compatibility study with the thiocolchicoside injection are reported in Tables 2–4. Table 2 shows colour, clarity and pH of the solutions of pharmaceutical products tested in this study. The results of the direct mixing of Miotens® with the other pharmaceutical injectable preparations are reported in Table 3.

The single pharmaceutical products showed pH values ranging from 4.4 to 9.1; Miotens® formulation pH was equal to 7.4. As shown in Table 3, Miotens® resulted compatible with Orudis® Soluzione i.m., Artrosilene® Fiale, Voltaren® Fiale Feldene® Fiale, Bentelan® 4 mg/2 ml Soluzione Iniettabile, Rexalgan®, Tora-dol® 30, Dobetin® 5000, Aspegic® 1000 Iniettabile, Mionevrasi® i.m. The colour, clarity and pH of the obtained mixture did not change significantly after mixing over 3 h. The pH variation observed in the mixture between Aspegic® 1000 and Miotens® during the testing period is attributable to the well known instability of acetylsalicylate, which leads to the hydro-

Table 2
Physicochemical characteristics of pharmaceutical products tested

Commercial name	Colour and clarity of the solution	pH
Miotens®	yellow, clear solution	7.4
Artrosilene® Fiale	colourless, clear solution	7.4
Orudis® Soluzione i.m.	colourless, clear solution	6.7
Voltaren® Fiale	colourless, clear solution	8.3
Feldene® Fiale	yellow, clear solution	8.3
Tora-Dol® 30	colourless, clear solution	7.5
Rexalgan®	intense yellow, clear solution	9.1
Aspegic® 1000 Iniettabile	pale yellow, clear solution	5.7
Mionevrasi® i.m.	fuchsia, clear solution	4.4
Bentelan® 4 mg/2 ml Soluzione iniettabile	colourless, clear solution	8.4
Dobetin® 5000	red, clear solution	4.9

lysis products acetic and salicylic acid. The mixture did not affect the hydrolysis of acetylsalicylate since it takes place also in the Aspegic® 1000 formulation alone maintained in the same conditions, as clarified by HPLC analysis.

After mixing Miotens® with all above mentioned drugs, pH of Miotens was not significantly changed after mixing, due to the presence of buffering agents in the Miotens® formulation. Moreover, thiocolchicoside remained in solution also at lower pH such as 4.8, for the Miotens®–Mionevrasi® mixture, and 5.3 for the Miotens®–Aspegic® 1000 mixture.

In Fig. 1 the pH of the single formulations is compared with the pH obtained after mixing with Miotens®. It is noteworthy that the pH values of the obtained mixtures are nearer to physiological pH than the single formulations, due to the presence of a buffer system in Miotens® formulation. The buffered Miotens® formulation ensures the maintenance of proper values of pH, more suitable for a safer i.m. administration. Aspegic® 1000 is not reported in the graph because of the variable pH values due to its intrinsic hydrolytic behaviour.

The results of the HPLC analysis of the mixtures at 0, 1 and 3 h after mixing are reported in Table 4. The HPLC analysis of the mixtures at time 0 and after 1 and 3 h from mixing, confirmed the formulation compa-

Table 3
Colour, clarity and pH of Miotens® injection mixed with different pharmaceutical products

Mixtures	Volume (ml)	Colour and clarity			pH		
		$t = 0$	$t = 1$ h	$t = 3$ h	$t = 0$	$t = 1$ h	$t = 3$ h
Miotens® + Artrosilene®	2+2	light yellow, clear solution	unchanged	unchanged	7.4	7.4	7.4
Miotens® + Orudis®	2+2	light yellow, clear solution	unchanged	unchanged	7.1	7.1	7.1
Miotens® + Voltaren®	2+3	light yellow, clear solution	unchanged	unchanged	7.7	7.7	7.7
Miotens® + Feldene®	2+1	light yellow, clear solution	unchanged	unchanged	7.7	7.7	7.7
Miotens® + Tora-dol® 30	2+1	light yellow, clear solution	unchanged	unchanged	7.5	7.5	7.5
Miotens® + Rexalgan®	2+2	yellow, clear solution	unchanged	unchanged	7.8	7.8	7.8
Miotens® + Aspegic® 1000	2+5	light yellow, clear solution	unchanged	unchanged	5.9	5.6	5.3
Miotens® + Mionevrasi®	2+3	light fuchsia, clear solution	unchanged	unchanged	4.8	4.8	4.8
Miotens® + Bentelan®	2+2	light yellow, clear solution	unchanged	unchanged	7.5	7.5	7.5
Miotens® + Dobetin® 5000	2+2	red, clear solution	unchanged	unchanged	6.8	6.8	6.8

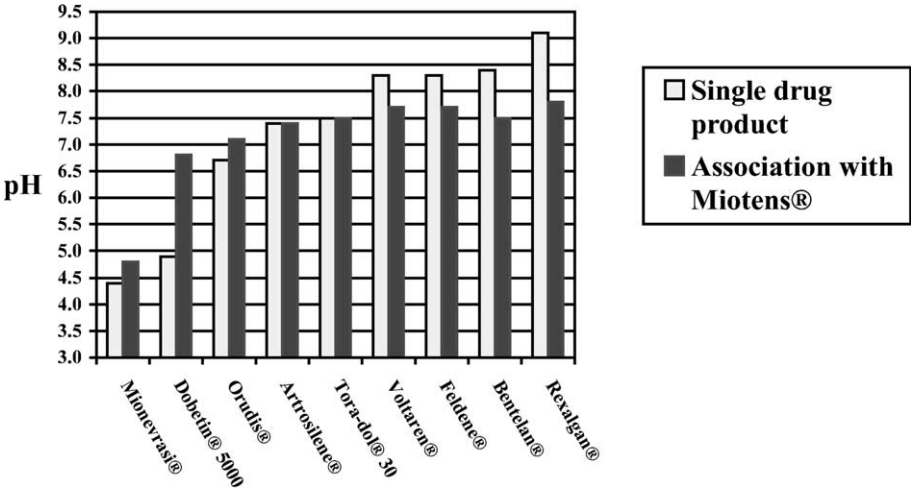

Fig. 1. Comparison between pH of the single formulations and of the mixtures.

Table 4
HPLC analysis of Miotens® injection mixed with different pharmaceutical products

Mixtures	Volume (ml)	Active drug	HPLC quantitative determination					
			$t = 0$		$t = 1$ h		$t = 3$ h	
			Concentrated (mg per dose)	% Content versus nominal value	Concentrated (mg per dose)	% Content versus nominal value	Concentrated (mg per dose)	% Content versus nominal value
Miotens® + Artrosilene®	2+2	thiocolchicoside	3.96	99.0	4.00	100.1	4.01	100.3
		ketoprofen	158.16	98.9	158.84	99.3	159.39	99.6
Miotens® + Orudis®	2+2	thiocolchicoside	3.97	99.2	4.03	100.7	3.99	99.9
		ketoprofen	101.23	101.2	100.72	100.7	100.38	100.4
Miotens® + Voltaren®	2+3	thiocolchicoside	4.00	100.0	4.03	100.8	4.05	101.3
		diclofenac	74.99	100.0	75.02	100.0	75.69	100.9
Miotens® + Feldene®	2+1	thiocolchicoside	3.97	99.2	3.98	99.5	3.97	99.3
		piroxicam	19.96	99.8	20.04	100.2	20.12	100.6
Miotens® + Tora-dol® 30	2+1	thiocolchicoside	4.05	101.2	4.07	101.7	3.98	99.6
		ketorolac	29.64	98.8	29.62	98.7	29.25	97.5
Miotens® + Rexalgan®	2+2	thiocolchicoside	4.10	102.4	4.13	103.3	4.13	103.3
		tenoxicam	20.71	103.6	20.82	104.1	20.75	103.7
Miotens® + Aspegic® 1000	2+5	thiocolchicoside	4.02	100.5	4.04	101.0	4.05	101.2
		acetylsalicylate	991.29	99.1	986.89	98.7	973.54	97.4
		salicylic acid		1.33 [a]		2.07 [a]		3.30 [a]
Miotens® + Mionevrasi®	2+3	thiocolchicoside	4.00	100.0	3.99	99.7	3.99	99.8
		vit. B_1	38.12	99.8	38.22	100.1	38.27	100.2
		vit. B_6	99.39	99.4	99.83	99.8	99.37	99.4
		vit. B_{12}	1.00	100.5	1.00	99.7	0.99	98.7
Miotens® + Bentelan®	2+2	thiocolchicoside	3.99	99.6	3.96	99.1	4.00	100.1
		betamethasone	4.00	100.0	3.97	99.2	4.00	100.1
Miotens® + Dobetin®	2+2	thiocolchicoside	4.02	100.5	4.01	100.2	4.00	100.1
		cyanocobalamin	5.0279	100.6	5.0203	100.4	5.0210	100.4

[a] % Area of salicylic acid versus acetylsalicylic acid.

tibility. In all the studied mixtures the content of thiocolchicoside and the associated active drug did not significantly change over the testing period. The obtained results showed that the content variations of all the active drugs remained well within 10% of their nominal values. Furthermore, there was no evidence of interaction/degradation products between the mixed drugs.

The time-dependent decrease of acetylsalicilate content observed in the Miotens®–Aspegic® 1000 mixture is due to the well known hydrolytic instability of this drug substance, which is not depending on Miotens®. In fact, Aspegic® 1000 formulation alone, under the same experimental conditions, underwent degradation to the same extent.

4. Conclusions

The combined therapies of Miotens® with antinflammatory drugs and vitamins based drugs (Orudis® Soluzione i.m., Artrosilene® Fiale, Voltaren® Fiale Feldene® Fiale, Bentelan® 4 mg/2 ml Soluzione Iniettabile, Rexalgan®, Tora-dol® 30, Dobetin® 5000, Aspegic® 1000 Iniettabile, Mionevrasi® i.m.) requires the evaluation of physicochemical compatibility of the extemporary mixture to be performed.

The observations and the measurements performed (colour, clarity, pH and content of active drugs) demonstrated the physicochemical compatibility of the extemporary mixtures of Miotens® with a number of anti-inflammatory and vitamin drugs.

References

[1] J.M. Janbroers, Review of the toxicology, pharmacodynamics and pharmacokinetics of thiocolchicoside, a GABA-agonist muscle relaxant with antinflammatory and analgesic action, Acta Ther. 13 (1987) 221–225.
[2] S.H. Yalkowsky, Formulation-related problems associated with intravenous drug delivery, J. Pharm. Sci. 87 (1998) 787–796.
[3] G. Pifferi, Compatibilità chimico-fisica tra tiocolchicoside e farmaci antinfiammatori non steroidei, Boll. Chim. Farm. 132 (1993) 203–209.
[4] M. Artusi, L. Maggi, P. Colombo, P. Pacifico, Physico-chemical compatibility between thiocolchicoside injection (MuscoRil®) and products usually used for combined therapy, Boll. Chim. Farm. Int. 11–12 (1998) 10–12.
[5] L.A. Frissel, Handbook of Injectable Drugs, ASHP Ed., Houston, 1990, pp. 12–22.