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(54) Titre : COMPOSITION PHARMACEUTIQUE A USAGE LOCAL CONTENANT UN AGENT CHOLINERGIQUE OU UN INHIBITEUR CALCIQUE

(54) Title: TOPICAL PHARMACEUTICAL COMPOSITION COMPRISING A CHOLINERGIC AGENT OR A CALCIUM CHANNEL BLOCKER

(57) Abrégé/Abstract:
A cholinergic agent and/or a calcium channel blocker is administered locally to the anus for the treatment of benign anal disorders, in particular anal fissures and haemorrhoids. The agents induce a reduction in the mean and resting pressure, thereby assisting in the healing of the anal fissures and haemorrhoids. Particularly preferred active agents are bethanechol and diltiazem, more particularly a combination thereof.

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(54) Title: TOPICAL PHARMACEUTICAL COMPOSITION COMPRISING A CHOLINERGIC AGENT OR A CALCIUM CHANNEL BLOCKER

(57) Abstract

A cholinergic agent and/or a calcium channel blocker is administered locally to the anus for the treatment of benign anal disorders, in particular anal fissures and haemorrhoids. The agents induce a reduction in the mean and resting pressure, thereby assisting in the healing of the anal fissures and haemorrhoids. Particularly preferred active agents are bethanechol and diltiazem, more particularly a combination thereof.

TOPICAL PHARMACEUTICAL COMPOSITION COMPRISING A CHOLINEGIC AGENT OR A CALCIUM CHANNEL BLOCKER

This invention relates to the use of diltiazem, alone or in combination with bethanechol, for the treatment of benign anal diseases where there is an associated anal sphincter spasm. The invention particularly relates to the treatment of anal fissures and painful haemorrhoidal conditions.

A fissure is a split in the skin of the distal anal canal. It is a common complaint in young adults with a roughly equal incidence in both sexes. Acute fissures are very common and most heal spontaneously, but a proportion progress to form a chronic linear ulcer in the anal canal and show great reluctance to heal without intervention.

Treatment has remained largely unchanged for over 150 years and the pathogenesis of anal fissure is not fully understood. The passage of a hard stool bolus has traditionally been thought to cause anal fissure. Thus for acute fissures the avoidance of constipation, such as involving a high bran diet, has been used as treatment for many years.

Anal dilators have also been involved in treatment. Typically a dilator of medium size was coated with anaesthetic jelly and inserted into the anal canal before the passage of stool to prevent exacerbation of the symptoms during defecation. The procedure was inconvenient and success rate was low. The most common treatment, for chronic anal fissures is a lateral internal sphincterotomy, which involves surgery to the

internal anal sphincter. This procedure, however, requires hospitalisation and leads in a sizeable number of patients to impairment of continence (British Journal of Surgery 1996, 83, 1334-1344). As yet there is no proven non-surgical treatment for chronic fissure, although local injection of botulinum A toxin shows early promise (Martindale, The Extra Pharmacopoeia 31st Edition p1516 and 1517).

A further potential non-surgical treatment that has recently been reported for anal fissures and haemorrhoids is the topical use of a nitric oxide donor, particularly glyceryl trinitrate. This reduces the internal anal resting pressure (British Journal of Surgery, 1994, 81, 1386-1389 and British Journal of Surgery, 1996, 83, 771-775 both by present inventors; Diseases of the Colon and Rectum, May 1995, p453-457, The New England Journal of Medicine Oct. 26, 1995, p1156 and 1157, WO-A-95/32715 and its equivalent US-A-5,504,117 - all by Gorfine; British Journal of Surgery 1996, 83, 776-777).

At a meeting of the Royal Society of Medicine Coloproctology Session on 27th November 1996, a paper entitled "The effect of alpha adrenoceptor blockade on the anal canal in patients with chronic anal fissure" was presented showing that indoramin reduced maximum resting pressures in the anal canal after 1 hour by 35.8% in patients with anal fissures. The author suggested a clinical trial to determine the efficacy of indoramin in the treatment of anal fissures.

In Dis Colon Rectum, February 1996, vol. 2, no.2, p212-216 nifedipine was reported as reducing the activity

of the internal anal sphincter in patients with high anal resting pressure, and was proposed for use in relieving symptoms in patients with haemorrhoids or anal fissures.

Haemorrhoids ('piles') are venous swellings of the tissues around the anus. Those above the dentate line (the point where the modified skin of the outer anal canal becomes gut epithelium), which usually protrude into the anal canal, are termed internal haemorrhoids, while those below this point are called external haemorrhoids. Due to internal pressure, internal haemorrhoids tend to congest, bleed and eventually prolapse; with external haemorrhoids painful thrombosis may develop.

Initial treatment of internal haemorrhoids involves a high-fibre diet and avoidance of straining at stool, so bulk laxatives and faecal softeners may be indicated. Small bleeding haemorrhoids may be injected with a sclerosing agent such as oily phenol injection, or they may be ligated with rubber bands. More severe and prolonged prolapse generally requires surgery. Surgical excision to remove the clot is used for thrombosed external haemorrhoids.

A range of mainly topical drug treatments is available for symptomatic relief, but in many cases their value is a best unproven. Local anaesthetics may be included to relieve pain, and corticosteroids may be used when infection is not present. Preparations containing either group of drugs are intended only for short-term use. Some preparations include heparinoids and other agents frequently included for their soothing properties

include various bismuth salts, zinc oxide, hamamelis, resorcinol and Peru balsam.

In British Journal of Surgery 1994, 81, 946-954, Loder *et al* reviewed the possible pathology, pathophysiology and aetiology of haemorrhoids but came to no firm conclusions. The authors speculate that the anal cushions surround the anal canal act as a seal to prevent minor leakage from the anus and these cushions distend as a consequence of haemorrhoidal disease. The authors also explored whether haemorrhoids is more prevalent in certain racial groups, whether it is a function of diet, habits or body habitus, whether it is a genetic disorder or whether it is associated with other conditions such as hernia. No firm conclusions were, however, reached as to the aetiology of haemorrhoids or how to treat it effectively.

Diltiazem is indicated orally for the treatment of angina pectoris and hypertension, and may be given intravenously in the treatment of arterial fibrillation or flutter and paroxysmal supraventricular tachycardia. Bethanechol is used as an alternative to catheterisation in the treatment of urinary retention, gastric atony and retention, abdominal distension following surgery, congenital megacolon, and oesophageal reflux. It is given in doses of 5mg subcutaneously or 10 to 50mg by mouth (Martindale, The Extra Pharmacopoeia, 31st Edition, p857 and p1417).

In a letter to the Lancet June 28, 1986 at p1493 and March 28, 1987 at p754 diltiazem given orally at 60mg was found to reduce internal anal resting pressure and to

treat proctalgia fugax. There was, however, no suggestion of diltiazem being used to treat anal fissure or haemorrhoids.

The object of the present invention is directed towards the provision of a non-surgical treatment for anal fissures and/or haemorrhoids, or other benign anal disorders.

The inventors have now found that anal fissures and haemorrhoids and other benign anal disorders can be treated by local application to the anus of diltiazem, alone or in combination with bethanechol. Other benign anal disorders would be those conditions associated with a high anal pressure or where there is an associated anal sphincter spasm.

Accordingly in a first aspect of the invention, there is provided use of diltiazem in the preparation of a medicament for local application to the anus for the treatment or prophylaxis of benign anal disorders.

A second aspect of the invention provides a composition adapted for local application in and around the anal canal for the treatment or prophylaxis of benign anal disorders associated with high anal pressure or anal sphincter spasm comprising diltiazem or a pharmaceutically acceptable salt thereof and bethanechol or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

By topical application we mean spreading a topical composition in and around the anal canal.

Without being bound by theory, it is believed that the diltiazem and bethanechol are at least partially effective (and there may be other mechanisms of action) by lowering the anal resting pressure of the patient. This helps the fissures to heal. This reduction in anal pressure should also allow better venous drainage which will allow the haemorroidal vascular cushions to heal.

In the case of haemorrhoids, it is also thought that bethanechol will act to contract the longitudinal muscle of the anus, thereby pulling the haemorrhoidal cushions back into place.

In any case the clinical results to date suggest the inventors have made a major advance in the field by providing a safe and efficacious non-surgical treatment for anal fissures and haemorrhoids.

By anal fissures we mean to include both acute and chronic fissures or ulcers. Any patient with persistent symptoms for more than two weeks is taken to have a chronic fissure in accordance with the invention.

By haemorrhoids we mean to include both internal and external haemorrhoids and acute thrombosis of external haemorrhoid (TEM).

Pharmaceutically acceptable salts of diltiazem and bethanechol, include those formed with both organic and inorganic acids. Such acid addition salts will normally

be pharmaceutically acceptable although salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. Thus, preferred salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, succinic, oxalic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, benzenesulphonic, and isethionic acids. Diltiazem hydrochloride, diltiazem malate and diltiazem have CAS registry numbers respectively as follows: 33286-22-5, 144604-00-2, and 42399-41-7. Bethanechol and bethanechol chloride have CAS registry numbers respectively of 674-38-4 and 590-63-6.

Diltiazem is of great benefit when topically administered separately, but diltiazem and bethanechol are of are of particular benefit and apparently exhibit a synergistic activity when administered together.

A suitable proportion of diltiazem in a topical composition for a beneficial effect is at least 0.5% w/w, such as 0.5% to 10% w/w, preferably 0.5% to 5% w/w, more preferably still 1% to 5% w/w, still more preferably 1% to 3%, and most preferably about 2%w/w. Preliminary dose ranging studies suggest that the maximum effect of the invention is obtained at about 2% and thereafter higher concentrations will not produce a substantial additional effect.

The diltiazem composition is suitably applied 3 to 6 times, preferably 3 to 4 times daily, which based on 8mg per application, gives a total daily dose of 24mg to 48mg.

A suitable proportion of bethanechol in a topical composition is at least 0.01% w/w, more preferably at least 0.05% such as 0.01% to 3% w/w, preferably 0.01% to 1% w/w, more preferably 0.05% to 1% w/w, and most preferably about 0.1% w/w. Preliminary dose ranging studies suggest that 0.1% w/w produced the maximum effect of the invention, and thereafter higher concentrations will not produce an additional effect.

The bethanechol composition is suitably applied in the same regimen as above which based on 0.4mg per application, gives a total daily dose of 1.2mg to 2.4mg.

Pharmaceutical compositions adapted for topical administration in and/or around the anal canal may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, foam, oils, aerosols, suppositories or enemas.

The topical compositions can comprise emulsifiers, preservatives, buffering agents and anti-oxidants. Preferably the compositions also comprise steroids (e.g. present at 0.1 to 5% w/w) such as prednisolone, busenonide or hydrocortisone, locally acting anaesthetics such as lignocaine (e.g. at 0.1 to 5% w/w), and soothants. Typical components used in existing fissure or haemorrhoidal treatments which can also be used in topical compositions of the invention include: zinc oxide, benzyl benzoate, bismuth oxide, bismuth subgallate and Peru balsam.

In accordance with the invention, the diltiazem or bethanechol can be administered in combination with trinitroglycerine or any other nitric oxide donor, isoprenaline, histamine, prostaglandin E_2, adenosine triphosphate, nictotine, DMPP, bradykinin, caerulein, glucagon, and phentolamine.

The topical composition may comprise skin penetrating agents, particularly the sulphoxides, such as dimethyl sulphoxide (DMSO) preferably at 25% to 50% w/w. Amides, (DMA, DMF) pyrrolidones, organic solvents, laurocaprom (AZONE) and calcium thioglycollate are suitable alternative penetrants. The composition may also optionally contain a polyacrylic acid derivative, more particularly a carbomer. This would both act as a skin hydrating agent to aid penetration of the drug, but also an emulsifying agent. The carbomer will help emulsify the DMSO, thereby mitigating skin irritation and providing enhanced skin hydration. Propylene glycol may also be present in the composition to soften the skin, increase thermodynamic potential and aid skin penetration by the DMSO and thus the drug. The final pH of the composition is advantageously pH 3.5 to 4.5.

The invention will now be described by way of example only with reference to the accompanying drawings, in which:-

Figure 1 is a graph of the dose response of diltiazem gel against mean anal resting pressure;

Figure 2 is a graph of duration of action of 1% w/w diltiazem gel against mean anal resting pressure;

Figure 3 is a graph of the dose response of bethanechol gel against mean anal resting pressure;

Figure 4 is a graph of duration of action of 0.1% w/w bethanechol gel against mean anal resting anal pressure; and

Figure 5 is a graph comparing 2% diltiazem, 0.1% bethanechol, and a combination of both over time against the reduction in mean anal resting pressure.

Example 1

A composition of base gel had the following composition: carmellose sodium 6g, polyethylene glycol 30ml, methylhydroxybenzoate 150mg, propylhydroxybenzoate 15mg, made up to volume with distilled water (pH6-7).

Various amounts of diltiazem and bethanechol were added in the amounts shown in Examples 4 and 6 to form various compositions for dose ranging studies.

Example 2

A base cream of the invention had the following composition:

Diltiazem hydrochloride (2% w/w)	10g
Dimethyl sulphoxide	250g
Carbomer 974P	5g
White soft paraffin	15g
Cetomacrogol emulsifying ointment*	115g
Propylene glycol	23g

Methylhydroxybenzoate (preservative soln.) To 500g
*composition: white soft paraffin 50g, liquid paraffin 20g, cetomacrogol emulsifying wax 30g (cetosteryl alcohol 24g and cetomacrogol 1000, 6g).

A base cream was formed by firstly separate mixing of the aqueous and non-aqueous components of the cream. Weighed quantities of propylene glycol and a proportion of the preservative solution were placed in a beaker to which the weight quantity of carbomer powder was added using an impeller type mixer to form a colloidal suspension of the carbomer. Thereafter, the weighed quantity of DMSO was added and rapid stirring continued at room temperature until a translucent uniform gel had been formed.

In the meantime, the weighed quantities of white soft paraffin and the cetomacrogol emulsifying ointment were placed in a separate beaker, heated to melting point and gently stirred to give a uniform base.

The drug is then added to the remainder of the preservative solution , which in turn was then added to the gel and whilst vigorously stirring, the uniform base (above) was added to form a cream. The carbomer acted as a dual neutralisation agent and primary emulsifier (of the oil and aqueous phases) to form the uniform cream base.

Example 3

A bethanechol cream composition was made up as above, but using 0.5g of bethanechol (0.1% w/w) instead of diltiazem.

Example 4 - Diltiazem Cream - Dose ranging study on healthy volunteers

Ten volunteers were used in a double blind study to determine the concentration of diltiazem cream (of Example 1) which most effectively lowers resting anal sphincter pressure as measured by an eight channel water perfused manometer. Concentrations of diltiazem cream used were 0.1%, 0.5%, 1%, 2%, 5% and 10%. Results showed a dose dependent reduction of the resting anal sphincter pressure. The maximal effect, at which the mean resting anal pressure was lowered by 28% ($P<0.0001$), was produced by 2% w/w cream (See Figure 1). Higher concentrations did not produce an additional effect. A typical 'one inch' application of the cream from the tube is equivalent to 8mg dose of diltiazem. Measurements taken throughout the day showed the effect of a single application to be sustained for 3 to 5 hours (see Figure 2).

Example 5 - Open Study of Diltiazem Cream in Patients with Anal Fissures

2% diltiazem cream from Example 2 was applied to the anus three times daily for 8 weeks to treat patients suffering from chronic anal fissures (in an uncontrolled, open, pilot study). To date, 7 patients were studied and followed up between 2 to 5 weeks. 5 patients have had

complete resolution of symptoms, of whom 3 have complete and 2 partial healing of the fissure. In four of these 5 patients there has been a reduction of the maximum resting anal sphincter pressure to within normal limits. The last patient, though symptom free, continues to have a high anal resting pressure.

2 patients had only had two weeks of treatment and one is symptom free after this short period, whilst the other still has occasional pain. It was too early to comment on healing of fissures in these two patients.

These results shows that diltiazem (applied topically) reduces the resting anal sphincter pressure in healthy and diseased patients. The preliminary open studies, albeit in a small group of patients, has shown a significant healing rate and symptom relief after only a few weeks application of both agents. This is a major achievement for the non-surgical treatment of fissures and offers hope to its many sufferers.

When the study of Example 4 was repeated using 60mg oral diltiazem once a day, no notable effect was obtained. At 60mg twice a day, the mean anal resting pressure was reduced by 17% (P=0.008), but two patients

notices postural dizziness. Topical diltiazem is safer and surprisingly more effective than oral diltiazem.

Example 6

In a combined bethanechol and diltiazem study, six healthy volunteers had topically applied to their anus on different days:

1) diltiazem at 2% w/w alone;
2) bethanechol at 0.1% w/w alone; and
3) diltiazem and bethanechol combined.

Anal mamometry was carried out before and after each of the three creams were applied and repeated at two hourly intervals. The mean results are shown in Figure 5.

These show that the combination of diltiazem and bethanechol gives a larger reduction in the mean anal resting pressure than either of diltiazem or bethanechol alone. This synergy may be due to both agents working in different mechanistic pathways to effect the pressure drop.

In summary, the results show that local application to the anus of diltiazem or diltiazem and bethanechol provides an efficacious treatment for benign anal disorder, particularly anal fissures and haemorrhoids. Furthermore since efficacy can be obtained at surprisingly low doses, the treatment of the invention is also substantially free of side effects normally associated with the active agents.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A composition adapted for topical application in and around the anal canal of a patient for the treatment or prophylaxis of benign anal disorders associated with high anal pressure or anal sphincter spasm comprising diltiazem or a pharmaceutically acceptable salt thereof and bethanechol or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

2. A composition as claimed in Claim 1, wherein diltiazem or a salt thereof is present in an amount of 2% to 5% w/w.

3. A composition as claimed in Claim 1 or Claim 2, wherein bethanechol or a salt thereof is present in an amount of 0.5% to 1% w/w.

4. A composition as claimed in any one of Claims 1 to 3, wherein bethanechol or a salt thereof and diltiazem or a salt thereof are present as the sole active components.

5. A composition as claimed in any one of Claims 1 to 3, which further comprises a steroid.

6. A composition as claimed in Claim 5, wherein in the steroid is present in the amount of 0.1% to 5% w/w.

7. A composition as claimed in Claim 5 or Claim 6, wherein the steroid is hydrocortisone.

8. A composition as claimed in any one of Claims 1 to 7 in the form of a gel, ointment, or cream.

9. Use of diltiazem or a pharmaceutically acceptable salt thereof in the preparation of a medicament for topical application in and around the anal canal of a patient for

the treatment or prophylaxis of benign anal disorders associated with high anal pressure or anal sphincter spasm.

10. A use as claimed in Claim 9, wherein the medicament contains diltiazem or a pharmaceutically acceptable salt thereof in an amount of 1% to 5% w/w.

11. A use as claimed in Claim 10, wherein the medicament contains diltiazem or salt thereof in an amount of 2% to 5% w/w.

12. A use as claimed in any one of Claims 9 to 11, wherein the medicament contains diltiazem or salt thereof as the sole active component.

13. A use as claimed in any one of Claims 9 to 11, wherein the medicament also contains bethanechol.

14. A use as claimed in Claim 13, wherein the bethanechol is present in an amount of 0.05% to 1% w/w.

15. A use as claimed in Claim 13 or Claim 14, wherein the medicament contains both bethanechol or a salt thereof and diltiazem or a salt thereof as the sole active components.

16. A use as claimed in any one of Claims 9 to 11, wherein the medicament also contains a nitric oxide donor, isoprenaline, histamine, prostaglandin E_2, adenosine triphosphate, nicotine, DMPP, bradykinin, caerulein, glucagon or phentolamine.

17. A use as claimed in any one of Claims 9 to 11, wherein the medicament also contains a nitric oxide donor.

18. A use as claimed in Claim 17, wherein the nitric oxide donor is trinitroglycerine.

19. Use of diltiazem or a pharmaceutically acceptable salt thereof and bethanechol or a pharmaceutically acceptable salt thereof in the preparation of a medicament for topical application in and around the anal canal of a patient for the treatment or prophylaxis of benign anal disorders associated with high anal pressure or anal sphincter spasm.

20. A use as claimed in Claim 19, wherein the diltiazem or pharmaceutically acceptable salt thereof is present in an amount of 2% to 5% w/w and bethanechol or pharmaceutically acceptable salt thereof is present in an amount of 0.05% to 1% w/w.

21. A use as claimed in Claim 19 or Claim 20, wherein the medicament contains diltiazem or pharmaceutically acceptable salt thereof and bethanechol or pharmaceutically acceptable salt thereof as the sole active components.

22. A use as claimed in any one of Claims 9 to 11, 13, 14, 19 and 20, wherein the medicament also contains a steroid.

23. A use as claimed in Claim 22, wherein the steroid is present in an amount of 0.1% to 5% w/w.

24. A use as claimed in Claim 22 or Claim 23, wherein the steroid is hydrocortisone.

25. A use as claimed in any one of Claims 9 to 25, wherein the medicament is for application to the internal anal sphincter of the patient.

26. A use as claimed in any one of Claims 9 to 25, wherein the benign anal disorder to be treated is haemorrhoids.

27. A use as claimed in any one of Claims 9 to 25, wherein the benign anal disorder to be treated is anal fissures.

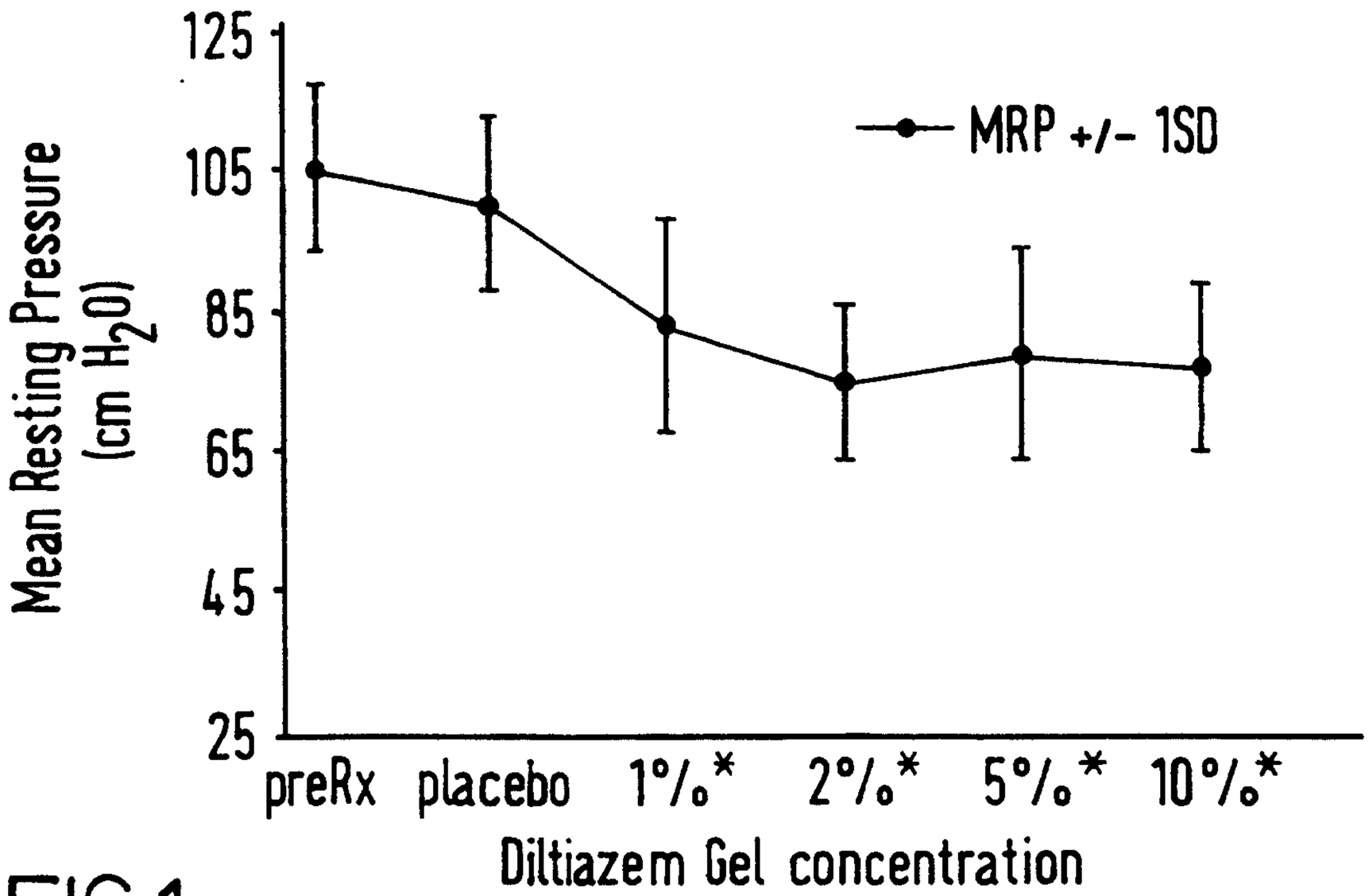
Diltiazem Gel: Dose-Response
125
105
85
65
45
25
Mean Resting Pressure (cm H_2O)
MRP +/- 1SD
preRx
placebo
1%*
2%*
5%*
10%*
Diltiazem Gel concentration

FIG.1

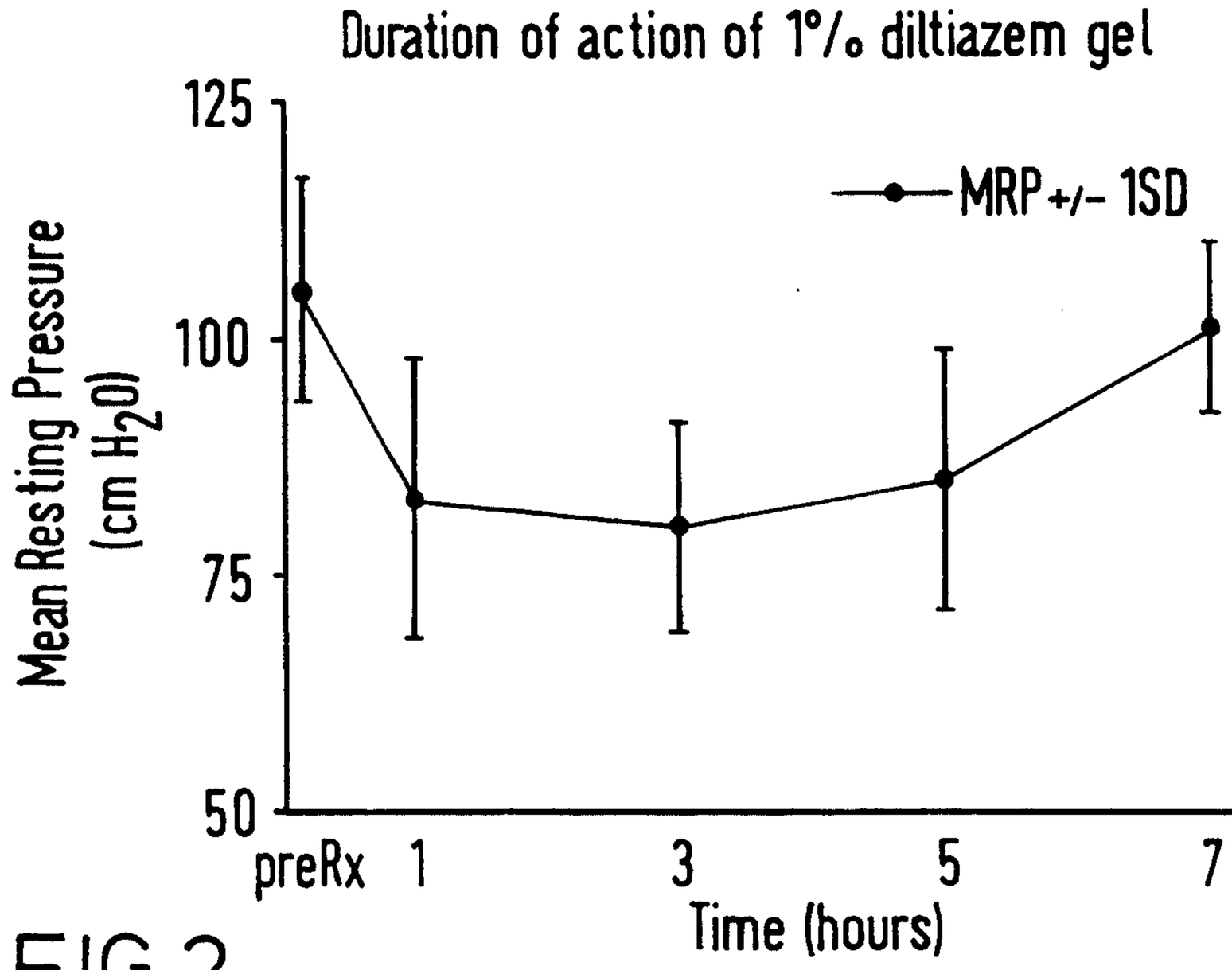
Duration of action of 1% diltiazem gel
125
100
75
50
Mean Resting Pressure (cm H_2O)
MRP +/- 1SD
preRx
1
3
5
7
Time (hours)

FIG.2

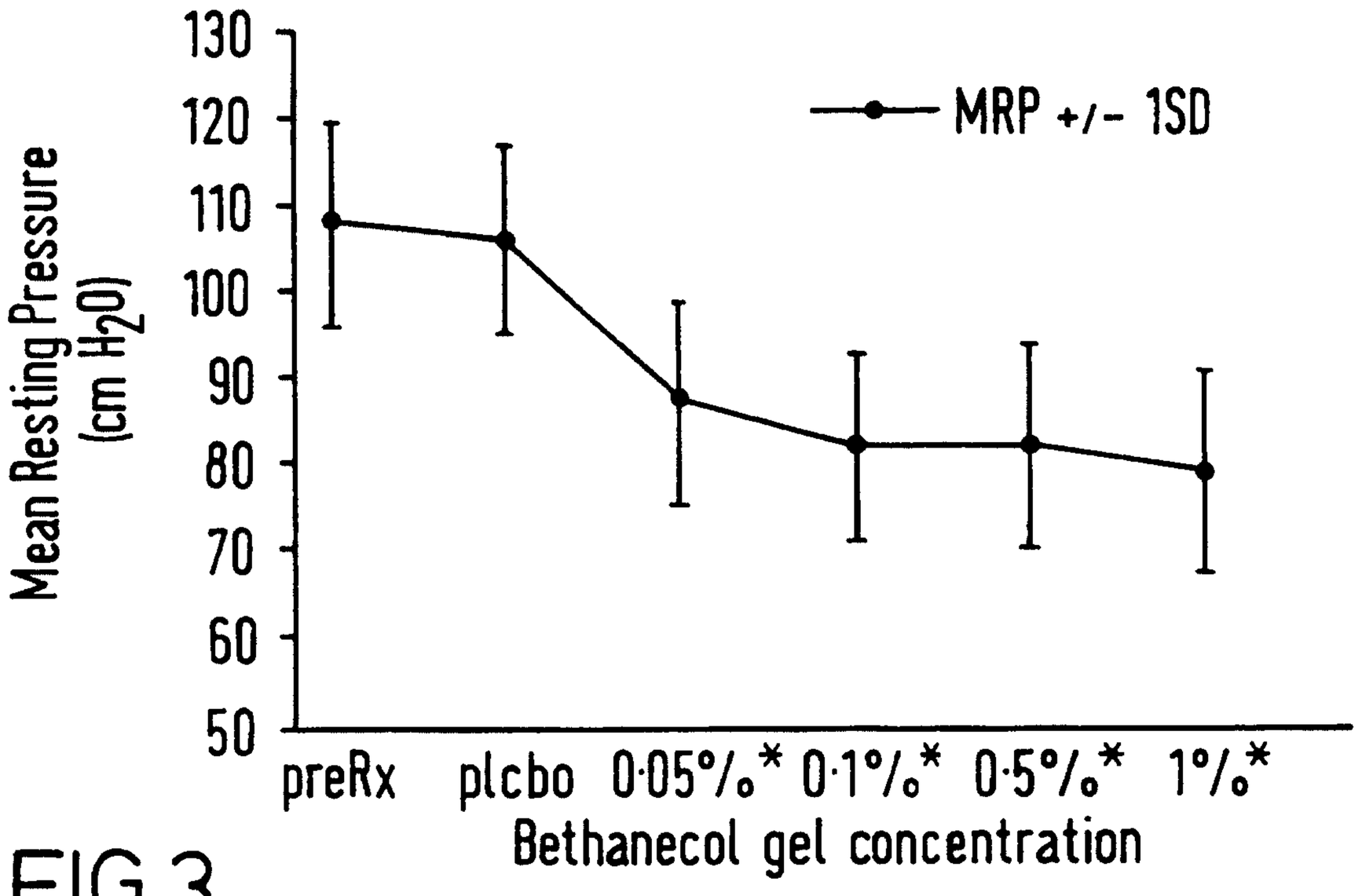
MRP +/- 1SD
Mean Resting Pressure (cm H_2O)
130
120
110
100
90
80
70
60
50
preRx
plcbo
0·05%*
0·1%*
0·5%*
1%*
Bethanecol gel concentration

FIG.3

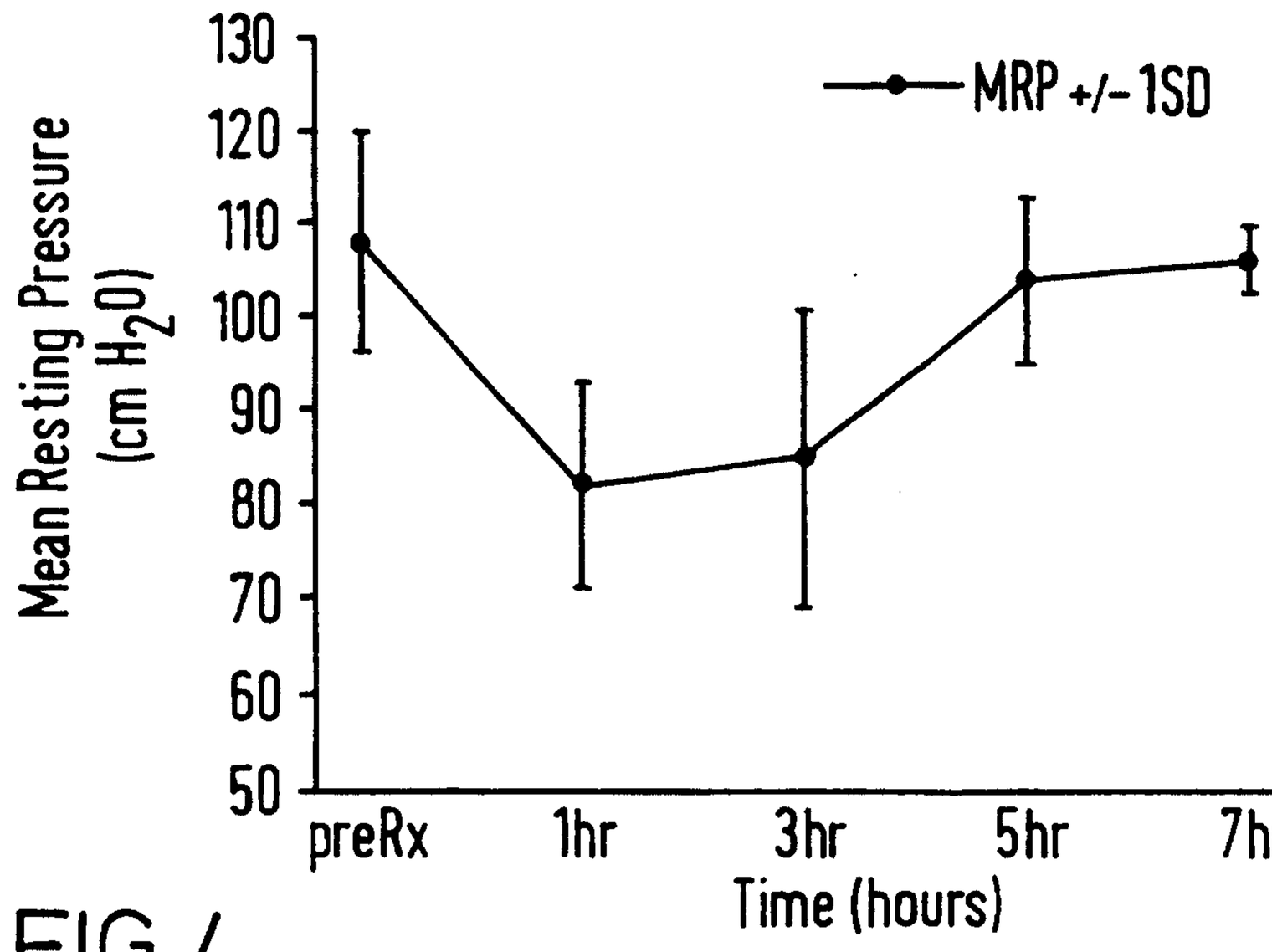
MRP +/- 1SD
Mean Resting Pressure (cm H_2O)
130
120
110
100
90
80
70
60
50
preRx
1hr
3hr
5hr
7hr
Time (hours)

FIG.4

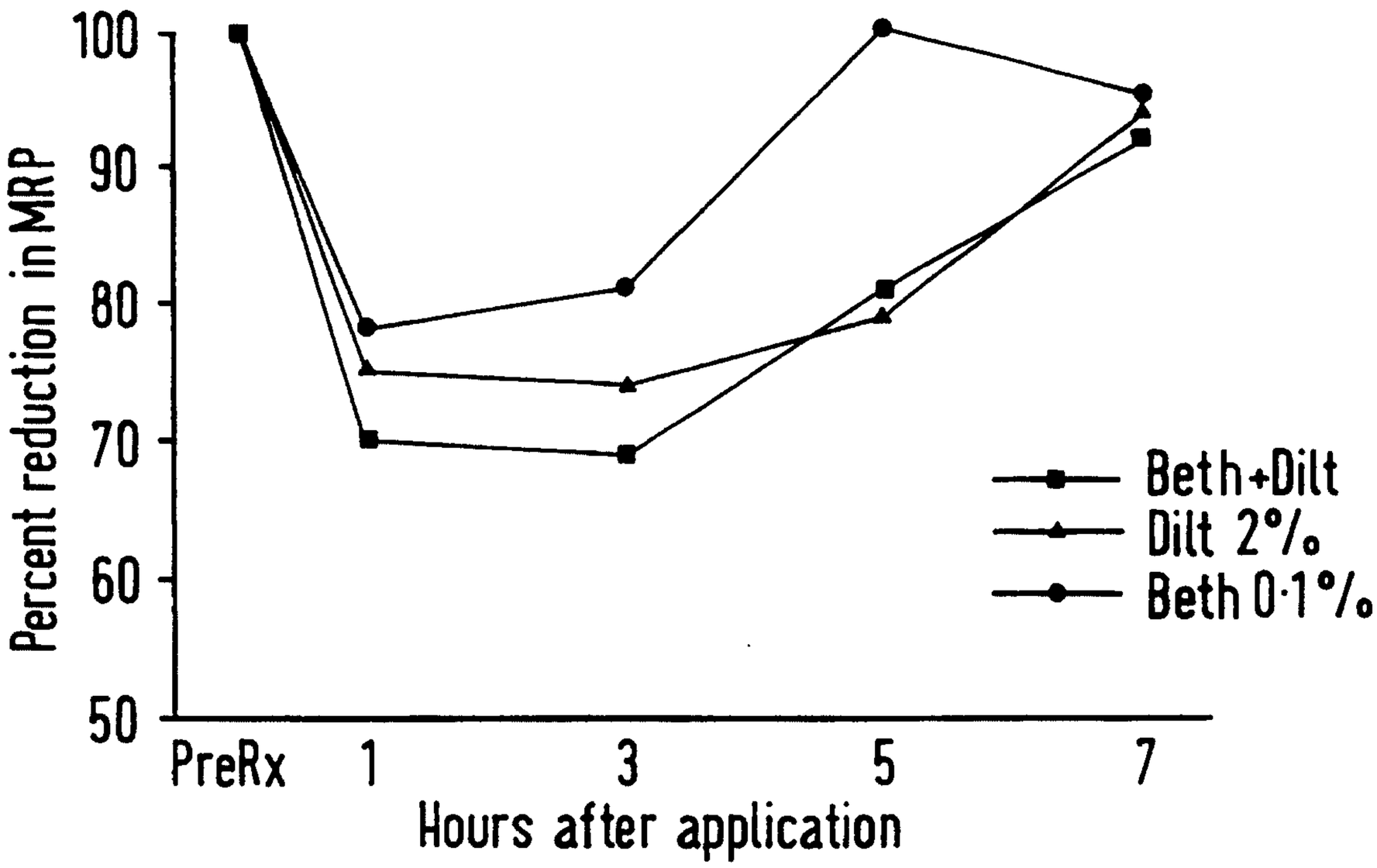
100
90
80
70
60
50
Percent reduction in MRP
PreRx
1
3
5
7
Hours after application
Beth+Dilt
Dilt 2%
Beth 0·1%

FIG.5