RECOMMENDATION

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In view of the present results, the following can be recommended:

1- Further experiments should be carried out to study the gastroprotective effect of different combinations of the studied drugs.

2- Clinical trials are needed to establish that:

   a. Rebamipide is a good choice to be given concurrently with ulcerogenic drugs like NSAIDs to gaurd against gastric insults.

   b. *Oleum cinnamomi* should be advised to be added as a food supplement for patients with history of PUD.

   c. Tianeptine, could be a good choice with particular importance for PUD patients who are under stress.

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PROTOCOL

A COMPARATIVE STUDY OF THE POSSIBLE PROTECTIVE EFFECTS OF REBAMIPIDE,TIANEPTINE, OLEUM CINNAMOMI ON ETHANOL-INDUCED AND INDOMETHACIN-INDUCED GASTRIC ULCER IN RATS

دراسة مقارنة للتأثير الوقائي المحتمل لأدوية الريباميبايد والتاينبتين وزيت القرفة على قرحة المعدة المستحدثة بالإيثانول والمستحدثة بالإندوميثاسين في الجرذان

Protocol of a thesis submitted
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لشروط الحصول على درجة
الماجستير في الفارماكولوجيا الإكلينيكية

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INTRODUCTION

Gastric ulcer is a multi-etiologic chronic disease. Ulcerogenic factors impair the balance between aggressive mechanisms (e.g. increased acid secretion) and protective mechanisms (e.g. healthy mucosa and bicarbonate secretion). Such ulcerogenic factors include: stress, trauma, sepsis, hemorrhagic shock, burns, pulmonary and liver diseases, helicobacter pylori, use of cigarettes and alcohol, and steroidal and non steroidal anti-inflammatory drugs.[1,2]

Moreover mucosal damage by oxygen free radicals has been associated with peptic ulcer and gastritis. The mechanism of damage involves lipid peroxidation, which destroys cell membranes with the release of intracellular components, such as lysosomal enzymes, leading to further tissue damage. These free radicals also promote mucosal damage by causing degradation of the epithelial basement membrane components, complete alteration of the cell metabolism and DNA damage.[3]

Gastric mucosal damage can be induced experimentally by ethanol. Ethanol causes hemorrhage, hyperemia, and loss of epithelial cells in the gastric mucosa through increaesed lipid peroxidation.[4]

Also mucosal injury can be elicited by indomethacin. Indomethacin acts as a non-selective inhibitor of the enzyme cyclooxygenase. Cyclooxygenase catalyses the formation of prostaglandins and thromboxane from arachidonic acid, which itself is derived from the cellular phospholipid bilayer by phospholipase A_2. Indomethacin, through inhibition of the formation of gastroprotective prostaglandins, can induce several changes in the gastric microenvironment (e.g., reduced gastric blood flow, reduced mucus and bicarbonate secretion, decreased cell repair and replication).[5]

There are several drugs available for treatment of gastric ulcer. However, they are frequently incompletely sufficient for controlling ulcer manifestations. Moreover, many of them are expensive and could have adverse effects not tolerated by all patients. Rebamipide, 2-(4-chlorobenzoylamino)-3-[2(1H)-quinolion-4-yl] propionic acid, is a new drug acting as an antioxidant by inhibiting lipid perioxidation in the gastric mucosa; and it was found to increase gastric mucosal prostaglandins by stimulating the biosynthesis of prostaglandin E_2-like substances.[6,7]

Many herbs and spices have been shown to impart antioxidant effects, the active principles are phenolics. Cinnamon is one of such traditional herbs that possess potent antioxidant, anti-inflammatory, anti-mutagenic, anti-carcinogenic, anti-tumour activities.[8] Such chemoprotective properties of cinnamon appear helpful in gastric ulcer disease.

Experimental studies have shown that some antidepressant drugs could be beneficial in gastric ulcer. A study performed on rats showed that imipramine dose dependently prevented cold-stress-induced gastric lesions. Another study has shown that serotonin–reuptake inhibitors could prevent 1-methly-4-phenyl-1,2,5,6- tetrahydropyridin (MPTP)-induced duodenal ulcer in rats.[9,10]

Nuclear factor-erythroid 2-related factor 2 (Nrf2) is a redox-sensitive transcription factor that regulates the expression of a variety of antioxidant and detoxification genes through an antioxidant-response element. Nrf2 has been shown to protect several types of cells against the acute and chronic injury that accompanies oxidative stress.[11] Nrf2 could therefore be involved in some protective mechanisms of antiulcer agents.

AIM OF THE WORK

The aim of the present work is to investigate the possible protective effects of Rebamipide (antioxidant), Tianeptine (antidepressant), *Oleum Cinnamomi* (herbal extract) on indomethacine- and ethanol-induced gastric ulcer in rats.

This will be conducted in view of correlation between these drugs and their effects on some oxidative stress parameters and the transcription factor Nrf2.

MATERIAL

The present work will be conducted on 72 male albino rats of body weight ranging from 160-180 gm.

The rats will be housed in animal cages, and will be kept under standard condtions of light and temperature with free access to food and water.

The following drugs will be used in the study.

- Rebamipide (antioxidant)
- Oleum Cinnamomi(herbal extract)
- Tianeptine(antidepressant)
- Indomethacin(ulcer inducer)
- Ethanol(ulcer inducer)

METHODS

Experimental groups and treatment:

Animals will be divided into 3 groups:

1. **Group 1: Control group:8 rats:**

   These animals will receive 5 ml/kg body weight of 2% gum acacia orally daily for 7 days as vehicle control of the studied drugs.

2. **Group 2:Ethanol induced gastric ulcer:**

   This group will be subdivided in to 4 groups each of 8 rats.

   2a: Control group:

   Animals will receive 5 ml/Kg body weight of 2% gum acacia orally daily for 7 days as vehicle control of the studied drugs. Then gastric lesion will be induced by oral administration of 1ml 50% ethanol for each rat on the 7^{th} day .

   2b: These animals will be treated with rebamipide 60 mg/kg body weight orally for 7 days and on the 7^{th} day induction of ulcer will done by giving 1ml 50% ethanol orally

   2c:These animals will be treated with *Oleum cinnamomi* 2.5 ml/kg body weight orally for 7 days and on the 7^{th} day induction of ulcer is done by giving 1ml 50% ethanol orally.

   2d: These animals will be treated with 12 mg/kg body weight Tianeptin orally for 7 days and on the 7^{th} day induction of ulcer is done by giving 1 ml 50% ethanol orally.

3. **Group 3:** Indomethacin induced gastric ulcer:

   This group will be subdivided into 4 groups each of 8 rats.

   3a: **Control group:** Animals will receive 5 ml/Kg body weight of 2% gum acacia orally daily for 7 days as vehicle control of the studied drugs.

Then gastric lesion will be induced by giving 100 mg /kg indomethacin orally.

3b: These animals will be treated with rebamipide 60 mg/kg body weight orally for 7 days and on the 7th day induction of ulcer will be done by giving 100 mg/kg indomethacin orally.

3c: These animal will treated with *Oleum cinnamomi* 2.5 ml/kg orally for 7 days and on the 7th day induction of ulcer will be done by giving 100 mg/kg indomethacin orally.

3d: These animal will treated with 12 mg/kg body weight Tianeptin orally for 7 days and on the 7th day induction of ulcer will be done by giving 100 mg/kg indomethacin orally.

4 hours after ulcer induction, the animals will be sacrificed .

The ulcer index will be calculated: the stomach will be cut along the lesser curvature and the mucosa is washed with cold saline, mucosa is scrubbed and stored at 20^0C until estimation of the chemical parameter.

The following parameters will be assessed:

1. Ulcer index and protective ratio. [12]
2. Glutathione perioxidase in gastric mucosa.[13]
3. Malondialdehyde in gastric mucosa.[14]
4. Superoxide dismutase in gastric mucosa.[15]
5. Nuclear factor erythroid related factor(Nrf2) in gastric mucosa.[11]

RESULTS

The results of this study will be tabulated and analyzed with the use of appropriate statistical methods and appropriate figures and diagrams.

DISCUSSION

The results will be discussed in view of achievement of the aim, their significance and their comparişon with previous related researchers.

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ARABIC SUMMARY

الملخص العربي

تعد قرحة المعدة والاثني عشر هي المرض ذو التأثير الاكلينيكي الاكبر بين امراض هذا الجزء من القناة الهضمية. وتتمحور الفيزيولوجيا المرضية لقرحة المعدة حول عدم التوازن بين العوامل الضارة والعوامل الوقائية التي يتعرض لها الغشاء المخاطي، والطريقة الأكثر فاعلية للتغلب علي هذه المشكلة هي استكشاف عوامل الخطر المرتبطة بها واستهدافها بالعلاج. في هذه الدراسة، تم استخدام نموذجي قرحة المعدة المستحدثة بالاندوميثاسين والايثانول في الجرذان لاختبار ومقارنة التأثيرات الوقائية لكل من الريبامايبيد، التيانبتين وزيت القرفة *في تطور* قرحة المعدة.

أجريت هذه الدراسة على اثنين وسبعين من ذكور الجرذان البيضاء تراوحت اوزانها بين ١٦٠-١٨٠ جرام. تم تقسيم الحيوانات عشوائيا إلى ثلاث مجموعات على النحو التالي:

١. المجموعة ١: مجموعة ضابطة: ٨ جرذان:

هذه الحيوانات تلقت ٥ مل / كجم وزن جسم ٢٪ من معلق الصمغ العربي عن طريق الفم يوميا لمدة ٧ أيام كاداة حاملة للأدوية محل الدراسة.

٢. المجموعة ٢: مجموعة قرحة المعدة المستحدثة بالايثانول (٣٢ جرذ):

تم تقسيم هذه المجموعة إلى أربع مجموعات فرعية في كل مجموعة ثمانية جرذان.

أ) مجموعة القرحة المعدية المستحدثة بالايثانول و غير المعالجة:

تلقت الحيوانات ٥ مل / كجم وزن جسم ٢٪ من معلق الصمغ العربي عن طريق الفم يوميا لمدة ٧ أيام كأداة حاملة للأدوية التي شملتها الدراسة، ثم تم في اليوم السابع استحداث قرحة المعدة بجرعة مفردة عن طريق الفم بمقدار ٧٠% ١مل ايثانول لكل جرذ.

ب) مجموعة القرحة المعدية المستحدثة بالايثانول، بعد العلاج بالريبامايبايد:

تم علاج الحيوانات باستخدام ريبامبايد ٦٠ مجم/كجم وزن جسم عن طريق الفم ولمدة ٧ أيام قبل استحداث القرحة بالايثانول.

ج) مجموعة القرحة المعدية المستحدثة بالايثانول، بعد العلاج بالتيانبتين:

تم علاج الحيوانات باستخدام تيانبتين ١٢ مجم/كجم وزن جسم عن طريق الفم ولمدة ٧ أيام قبل استحداث القرحة بالايثانول.

د) مجموعة القرحة المعدية المستحدثة بالايثانول، بعدالعلاج بزيت القرفة:

تم علاج الحيوانات باستخدام زيت القرفة ٢.٥ مجم/كجم وزن جسم عن طريق الفم ولمدة ٧ أيام قبل استحداث القرحة بالايثانول.

٣) المجموعة ٣: القرحة المعدية المستحدثة بالاندوميثاسين (٣٢ جرذ):

تم تقسيم هذه المجموعة إلى ٤ مجموعات فردية كل واحدة تحتوى على ٨ جرذان.

أ) مجموعة القرحة المعدية المستحدثة بالاندوميثاسين وغير المعالجة:-

تلقت الحيوانات ٥ مل / كجم من وزن الجسم ٢٪ من معلق الصمغ العربي عن طريق الفم يوميا ولمدة ٧ ايام على اعتباره اداة حاملة للادوية محل الدراسة، ومن ثم تم استحداث الاصابة المعدية بجرعة فردية من الاندوميثاسين عن طريق الفم مقدارها ١٠٠مجم/ كجم.

بدأنا في دراسة تجريبية منفصلة مع جرعات صغيرة ٢٠ و ٣٠ و ٥٠ ملجم / كجم لكنها لم تعط التأثير، ثم قمنا بزيادة الجرعة، وحصلنا على تأثير بجرعة ١٠٠ ملجم / كجم.

ب) مجموعة قرحة المعدة المستحدثة بالاندوميتاسين، بعد العلاج بالريبامبايد:

تم علاج الحيوانات بريبامبيد ٦٠ ملجم / كجم من وزن الجسم عن طريق الفم يوميا لمدة ٧ أيام قبل استحداث القرحة بالاندوميثاسين.

ج) **مجموعة قرحة المعدة المستحدثة بالاندوميتاسين، بعد العلاج بالتيانيبتين:**

تم علاج الحيوان بتيانبتين ١٢ ملجم / كجم عن طريق الفم يوميا لمدة ٧ أيام قبل استحداث القرحة بالإندوميتاسين.

د) مجموعة القرحة المعدية المستحدثة بالاندوميتاسين، بعد العلاج بزيت القرفة:

تم علاج الحيوانات بزيت القرفة مقدار ٢.٥ملجم/كجم عن طريق الفم يوميا لمدة سبعة ايام قبل استحداث القرحة بالاندوميتاسين.

في نهاية فترة التجربة تم تخذير الحيوانات واستئصال المعدة في كل منها الحيوانات ثم وضعت كل معدة في كوب مملوء بملح فسيولوجي ثلجي بارد، ومن ثم تم تجفيفه بعناية. فتحت المعدة على طول الانحناء الأكبر، ومن ثم تم تقييم مؤشر القرحة ونسبة الحماية على أساس قطر الاصابة ثم أزيل الغشاء المخاطي باستخدام شريحة زجاجية تمت مجانسته ثم وضع في جها الطرد المركزي ثم اخذت المادة الطافية وجمدت في درجة حرارة-٢٠ C وذلك لتقييم المعاملات التالية:

* السوبراوكساید دسميوتيز.
* مالون داي الديهايد.
* جلوتاثيون بيروكسيديز.
* عامل Nrf2.

وكانت نتائج الدراسة كالاتي:

أ) **تأثير كل من الريبامبايد ،التيانبتين، وزيت القرفة على القرحة المعدية المستحدثة بالاندوميثاسين في الجرذان:-**

١- التأثير على مؤشر القرحة :

انخفض مؤشر القرحة بشكل ملحوظ في جميع المجموعات التي خضعت للعلاج بالادوية محل الدراسة بالمقارنة مع مجموعة الاندوميثاسين الضابطة.

- وكان المتوسط ± الخطأ المعياري لمؤشر القرحة في مجموعة الاندوميثاسين الضابطة ١٣ ± ١,٠٢ بينما في المجموعة السابق علاجها بـالريبامبايد، التيانبتين وزيت القرفة كان ٣,٥ ± ٠,٧١، ٩,٨٨ ± ٠,٦٤ و ٧ ± ٠,٩٣ مع نسب حماية ٧٤٪، ٢٥٪ و ٤٦٪ على التوالي.

٢-التأثير على السوبر اوكساید دسميوتيز:

كانت هناك زيادة كبيرة في نشاط السوبراوكساید ديسميوتيز في جميع المجموعات المعالجة السابق علاجها بالمقارنة مع مجموعة الاندوميثاسين الضابطة. كان المتوسط ± الخطأالمعياري في المجموعات السابق علاجها بالريبامبايد،التيانبتين وزيت القرفة كان ٥,٩٦ ± ٠,٢٧، ٥,٦٥ ± ٠,٢٣ و ٤,٧٢ ± ٠,٤٣ وحدة / جم على التوالي مقابل ٣,٠٦ ± ٠,٦٢ وحدة/ جم في مجموعة الاندوميثاسين الضابطة.

٣-التأثير على مالون داي الديهايد:

كان هناك انخفاض في محتوى مالون داي الديهايد في المجموعات السابق علاجها بالتيانبتين وزيت القرفة مقارنة مع مجموعة الاندوميثاسين الضابطة. وكان المتوسط ± الخطأ المعياري ٢٣٨,٣٨±٢١,٧١ و ٢١٧.٦٦ ± ١٢.٢١ نانومول/ جم على التوالي مقابل ٣٨٨.٠٠ ± ٢٧.٢٢ نانومول / جم في مجموعة الاندوميثاسين الضابطة ، في حين كانت هناك تغييرات ضئيلة في المجموعة السابق علاجها بالريباميباید.

٤- التأثير على الجلوتاثيون بيروكسديز:

كانت هناك زيادة كبيرة في نشاط جلوتاثيون بيروكسديز بالغشاء المخاطي بالمعدة في كل المجموعات المعالجة مقارنة بمجموعة الاندوميثاسين الضابطة. المتوسط ± الخطأالمعياري كان في المجموعات المعالجة بالريباميباید، التيانيبتين وزيت القرفة هو : ٦٦,٧٥ ± ٥,٩٥، ٥١,٦٣ ± ٢,٨٩ و ٤٥,٨١ ± ٣,٦٣ وحدة / جم على التوالي مقابل ١٦,٣٥ ± ١,٠١ وحدة / جم في مجموعة الاندوميثاسين الضابطة.

٥- التأثير على عامل (Nrf2):

لوحظ انخفاض كبير في مستوي عامل Nrf2 بالغشاء المخاطي بالمعدة مقارنة بمجموعة الاندوميثاسين الضابطة. كان المتوسط ± الخطأالمعياري في المجموعات المعالجة بالريباميباید، التيانيبتين وزيت القرفة ١٢٦,٥٨ ± ١٠,٩٦، ١١٧,٥٠ ± ٤,٨٢ و ١١٢,٥٤ ± ١١,١٩ نانوجرام / مل على التوالي مقابل ٢٠٦,١٣ ± ١١,٤٩ نانوجرام / مل في مجموعة الاندوميثاسين الضابطة.

ب) تأثير الريبامبياید والتيانبتين وزيت القرفة على القرحة المعدية المستحدثة بالايثانول في الجرذان:-

١) التأثير على مؤشر القرحة :

كان هناك انخفاض كبير في مؤشر القرحة في كل المجموعات التي خضعت للعلاج بالادوية محل الدراسة مقارنة بمجموعة الايثانول الضابطة.

وكان المتوسط ± الخطأالمعياري لمؤشر القرحة في مجموعة الإيثانول الضابطة٢٦,٨٨ ± ٢,٢٩ بينما في المجموعة المعالجة تمهيديا بالريبامبياید، التيانيبتين وزيت القرفة: ٧.٧٥ ± ٠,٦٥، ١٣,٥٠ ± ٠,٩٨ و ١٠,٧٥ ± ١,٠ مع نسب وقائية من ٧٢٪، ٤٨٪ و ٦٠٪ على التوالي.

٢- التأثير على السوبر اوكساید دسميوتيز:

كانت هناك زيادة كبيرة في نشاط السوبراوكساید ديسميوتيز في المجموعة السابق علاجها بزيت القرفة وكان المتوسط ±الخطأالمعياري هو٦,٦٣ ±٠,٩٤ وحدة / جم في مقابل٢,٦٩ ±٠,٧٣ وحدة / جم في مجموعة الايثانول الضابطة.

٣-التأثير على مالون داي الديهايد:

كان هناك انخفاض كبير في محتوى مالون داي الديهايد في كل المجموعات السابق علاجها بالادوية محل الدراسة مقارنة بمجموعة الايثانول الضابطة. كان المتوسط ± الخطأالمعياري في المجموعات المعالجة بالريباميباید، التيانيبتين وزيت القرفة في هو ١٤٣,٦٣ ± ٧,٨٤، ١٦٣,٧٥ ±

٩,٠١ و ١٨٣,٩١ ± ٣٧,٥٦ نانومول / جم على التوالي مقابل ٣٢١,٢٥ ± ١٢,٠٢ نانومول / جم في مجموعة التحكم بالايثانول.

٤-التأثير على الجلوتاثيون بيروكسيديز:

كانت هناك زيادة كبيرة في نشاط جلوتاثيون بيروكسيديز في المجموعات السابق علاجها بالريباميباید والتيانيبتين ـ مقارنة بمجموعة الايثانول الضابطة. وكان المتوسط ± الخطأالمعياري في المجموعات السابق علاجها بالريباميباید والتيانيبتين هو : ٧٥,٦٩±٤,٨٤و ٦٥,٦٦ ± ٥,٣٢ وحدة/جم على التوالي مقابل ١٨,٤٩ ± ٢,٧٦ وحدة / جم في مجموعة الايثانول الضابطة. من ناحية أخرى، لم يلاحظ اي تغييرات ذات قيمة معنوية في المجموعة السابق علاجها بزيت القرفة.

٥-التأثير على عامل (Nrf2):

بالغشاء المخاطي للمعدة في كل المجموعات السابق Nrf2 لوحظ وجود انخفاض كبير في مستوي علاجها بالادوية محل الدراسة مقارنة بمجموعة الايثانول الضابطة. وكان المتوسط ± الخطأالمعياري ±في المجموعات السابق علاجها بالريباميباید، التيانيبتين وزيت القرفة هو٧٠,١٣ ±٦,٤٣، ٧٤,٥٩ ٣,٣١و ٩٣,٤٦ ± ٣,١٠ نانوجرام / مل على التوالي مقابل ١٦٥,١١ ± ١١,١١ نانوجرام / مل في مجموعة الايثانول الضابطة.

الملخص العربى

لجنة الإشراف

أ.د. مرفت كامل بركات .....
أستاذ الفارماكولوجيا الإكلينيكية
كلية الطب
جامعة الإسكندرية

د. عمرو عبد القادر عقدة .....
أستاذ مساعد الفارماكولوجيا الإكلينيكية
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مشرف مشارك
د. دعاء علي عبد المنصف .....
مدرس كيمياء حيوية طبية
كلية الطب
جامعة الإسكندرية

دراسة مقارنة للتأثير الوقائي المحتمل لأدوية الريبامبيايد والتاينبتين وزيت القرفة على قرحة المعدة المستحدثة بالإيثانول والمستحدثة بالإندوميثاسين في الجرذان

مقدمة من

شهرزاد عبد المجيد يوسف القزيطي

بكالوريوس الطب والجراحة - جامعة الزاوية

للحصول على درجة

الماجستير

فى

الفارماكولوجيا الإكلينيكية

لجنة المناقشة والحكم على الرسالة	**موافقون**
أ. د / مصطفى عبد العزيز محمد أستاذ الفارماكولوجيا كلية الطب البيطرى جامعة كفر الشيخ	.....
أ. د / ميرفت كامل بركات أستاذ الفارماكولوجيا الإكلينيكية كلية الطب جامعة الإسكندرية	.....
د / إيناس السيد درويش أستاذ مساعد الفارماكولوجيا الإكلينيكية كلية الطب جامعة الإسكندرية	.....

دراسة مقارنة للتأثير الوقائي المحتمل لأدوية الريباميباید والتاينبتين وزيت القرفة على قرحة المعدة المستحدثة بالإيثانول والمستحدثة بالإندوميثاسين في الجرذان

رسالة

مقدمة الي الفارماكولوجيا الإكلينيكية – كلية الطب – جامعة الأسكندرية
إستيفاء للدراسات المقررة للحصول على درجة

الماجستير

فى

الفارماكولوجيا الإكلينيكية

مقدمة من

شهرزاد عبد المجيد يوسف القزيطي

بكالوريوس في الطب والجراحة- كلية الطب- جامعة الزاوية

قسم الفارماكولوجيا الإكلينيكية – كلية الطب

جامعة الإسكندرية

٢٠١٤