Possible Modulatory Effect Of Bee Venom On Methotrexate Efficacy And Pharmacokinetics In A Model Of Experimentally Induced Arthritis.

Thesis presented by

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بسم الله الرحمن الرحيم

وَأَوْحَىٰ رَبُّكَ إِلَى ٱلنَّحْلِ أَنِ ٱتَّخِذِى مِنَ ٱلْجِبَالِ بُيُوتًا وَمِنَ
ٱلشَّجَرِ وَمِمَّا يَعْرِشُونَ ﴿٦٨﴾ ثُمَّ كُلِى مِن كُلِّ ٱلثَّمَرَٰتِ فَٱسْلُكِى سُبُلَ رَبِّكِ
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فِى ذَٰلِكَ لَءَايَةً لِّقَوْمٍ يَتَفَكَّرُونَ ﴿٦٩﴾

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Abstract

ABSTRACT

Background: Low dose methotrexate is the cornerstone for the treatment of rheumatoid arthritis. One of its major drawbacks is hepatotoxicity, resulting in poor compliance of therapy. **Objective:** The present study was aimed to investigate the modulatory effect of bee venom on efficacy, toxicity, pharmacokinetics and tissue disposition of methotrexate. **Methods:** Complete Freund's adjuvant induced arthritic rats were treated with methotrexate and/or bee venom. Arthritic score, ankle diameter, paw volume and tissue TNF-α were determined to assess anti-arthritic effects, while anti-nociceptive effects were assessed by gait score and thermal hyperalgesia. Liver enzymes and serum TNF-α were also evaluated. In addition, a single intra-peritoneal dose of methotrexate was injected into non arthritic rats alone or preceded with bee venom. Methotrexate concentrations in plasma, synovial fluid and different tissues were determined. **Results:** Combination therapy of bee venom with methotrexate significantly improved arthritic parameters and analgesic effect as compared to methotrexate alone. Bee venom ameliorated the serum TNF-α and liver enzymes elevations induced by Methotrexate. Histopathological examination supported the role of bee venom in alleviating methotrexate induced hepatotoxicity. In addition, Bee venom increased methotrexate bioavailability with a significant decrease in the latter elimination. **Conclusion:** Bee venom potentiates the anti-arthritic effects of methotrexate,

possibly by increasing its bioavailability. In addition, it provides a potent anti-nociceptive effect in adjuvant induced arthritic model. Furthermore, bee venom protects against methotrexate induced hepatotoxicity mostly due to its inhibitory effect on TNF-α.

Keywords: Bee Venom - Methotrexate - Adjuvant arthritis - TNF-α - Pharmacokinetics.

Appendix

List of Contents

List of Abbreviations

AA	Adjuvant arthritis
ACR	The American College of Rheumatology
AICAR	5-aminoimidazole-4-carboxamide ribonucleotide
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	The area under the plasma concentration-time curve
BALB/c	Albino, laboratory-bred strain of the House Mouse
BB-DR	spontaneous diabetes-resistant bio-breeding strain
BN	Black Norwegian strain
BV	Bee venom
CAM	Complementary and Alternative Medicine
CFA	Complete Freund's adjuvant
CIA	Collagen-induced arthritis
CL	Total body clearance
C_{max}	Maximum concentration
DA	Sprague-Dawley rat strain

DBA	Dilute, brown and non-Agouti mouse strain
DMARDs	Disease modifying anti-rheumatic drugs
EULAR	European league against rheumatism
F344	Fisher 344 strain
H&E	Hematoxylin and eosin stain
HCl	Hydrochloric acid
HPLC	High performance liquid chromatography
i.p.	Intra-peritoneal
IFA	Incomplete Freund's adjuvant
IL	Interleukin
K_{el}	The elimination rate constant
LA/N	Derived from a cross of the spontaneously hypertensive Sprague-Dawley rat strains and was hypertensive, hyperlipidemic, and prone to fulminant atherosclerosis.
LEW	Lewis strain
LOU/MN	Rat of Wistar origin kept at Univerisite Catholique de Louvain with low immunocytoma.
MRT	Mean resident time
MTX	Methotrexate
MTXPGs	Methotrexate polyglutamate derivatives

NSAIDs	Non steroidal anti-inflammatory drugs
NSD/N	Rats developed at NIH, Sprague -Dawley and slow acetylators.
OAT-K1	Organic anion transporter K1
PLA2	Phospholipase A2
PWL	Paw withdrawal latencies
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RFC1	Reduced folate carrier 1
s.c.	Subcutaneous
SCW	Streptococcal cell wall-induced arthritis
SD	Standard deviation
$t_{1/2}$	Elimination half life
TNF-α	Tumor necrosis factor-alpha

List of Tables

List of Figures