Equivalent Intraperitoneal to Orally Administered Doses of Ibuprofen on Dose Response Curve for Analgesia and Prostaglandin Inhibitory Effect in Mice

Thesis submitted for partial fulfillment of M.Sc. in Pharmacology.

By

Raghda Abd el Aziz Mohammed Salama

MB. BCh. 2009

Supervised by

Prof. Sonia Salib Georgy

Professor of pharmacology

Faculty of Medicine - Ain Shams University

Dr. May Ahmed Amin Hamza

Assistant Professor of pharmacology

Faculty of Medicine - Ain Shams University

Dr. Nesreen Hamdy Lotfy El gayar

Lecturer of pharmacology

Faculty of Medicine - Ain Shams University

Faculty of Medicine

Ain Shams University

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AD	Alzheimer's disease
ADP	adenosine diphosphate
ANOVA	Analysis of variance
AUC	area under the curve
BCG	Bacillus Calmette-Guérin
BW	Body wieght
cAMP	Cyclic adenosine mono phosphate
CGRP	calcitonin gene-related peptide
COX	cyclooxygenase
coxibs	selective COX-2 inhibitors
CYP	Cytochrome P450 enzymes
DAG	diacylglycerol
DRG	dorsal root ganglia
ECM	extracellular matrix
EIA	Enzyme Immunoassay
ELISA	enzyme-linked immunosorbent assay
ERPF	effective renal plasma flow
GFR	glomerular filtration rate
i.p.	intraperitoneal
IC50	Inhibitory concentration
IL-1β	interleukin 1β
IL-6	interleukin 6
IP3	inositol triphosphate
kD	kilodalton
LD	lethal dose

log	logarithm
LOX	lipoxygenases
NO	nitric oxide
NSAIDs	Non steroidal anti-inflammatory drugs
OTC	over the counter
PGE_2	prostaglandin E_2
PGI_2	prostacyclin
PGs	prostaglandins
PKA	protein kinase A
PLC	Phospholipase c
PRB	pain related behaviour
S.C.	subcutaneous administration
S.E.M	standard error of the mean
S1P	Sphingosine 1-phosphate
SD	standard deviation
TNFα	tumor necrosis factor-α
TTX	tetrodotoxin
TX	thromboxane
vWF	Von Willebrand factor

Non steroidal anti-inflammatory drugs

For centuries, non steroidal anti-inflammatory drugs (NSAIDs) have been part of clinical practice. NSAIDs originally used as drugs with anti-inflammatory and analgesic effect, are now used for new therapeutic targets, some of which are unrelated to their primary mode of action. NSAIDs, as a group, have expanded to include a large number of compounds, supporting their efficacy in the treatment of different pathologies ranging from pain and inflammation to prevention and treatment of cancer **(Pountos et al., 2011)**.

Hippocrates, the father of modern medicine, was the first to record descriptions of therapeutic benefits of extracts of willow bark and other plant sources of salicylates, 2400 years ago. He recommended chewing willow leaves for analgesia during labour and the juice of the poplar tree for eye diseases **(Mueller and Scheidt, 1994)**. There was no real progress in the synthesis and use of NSAIDs until the chemical synthesis of salicylic and acetylsalicylic acids by Charles Gerhardt in 1853 and in 1897 by Felix Hoffmann **(Rainsford, 2007; Mullar and Scheidt, 1994)**. Indomethacin and ibuprofen were developed in the 1960s. As ibuprofen is approved as over-the-counter drug, it is widely used **(Rainsford, 2007)**. A large number of NSAIDs have been introduced in recent years and a second breakthrough in the

development of NSAIDs was the discovery of the cyclo-oxygenase-2 (COX-2) isoform and the development of the selective COX-2 inhibitors (coxibs) at the beginning of the 21st century ***(Rainsford, 2013).***

Naturally, with the large number of NSAIDs in the market and post marketing surveillances, many of them have been withdrawn or have disappeared from the market ***(Rainsford, 2013)***. However, NSAIDs remain of the most commonly used medications, with approximately 70% of people aged 65 years or older are reported to use NSAIDs at least once per week ***(Talley et al., 1995)***. In the US alone, prescriptions for NSAIDs exceed 111 million every year, with an approximate cost of $4.8 billion **(Laine, 2001)**.

Various types of NSAIDs

Despite the differences in their chemical structures, NSAIDs share many properties especially in their use as analgesics. For example, all NSAIDs have a ceiling effect that limits their efficacy in severe increasing pain. Studies failed to clearly classify NSAIDs in-terms of efficacy, since patient response to NSAIDs varies. In other words, if a patient does not respond to an NSAID, other NSAIDs can be tried. In most cases, the side-effects profile will determine NSAID selection rather than minor differences in efficacy **(Green, 2001).**