THE PARADOX OF HUMAN EQUIVALENT DOSE FORMULA – A CANONICAL CASE STUDY OF PIROXICAM (FELDENE) IN MONOGASTRIC ANIMALS

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PIROXICAM IS A NON-STEROIDAL ANTI-INFLAMMATORY ANALGESIC THAT CAN CAUSE ALCERATION OF MUCOSAL LINING AND BLEEDING OF GASTROINTESTINAL TRACT. IT IS ALSO TOXIC TO KIDNEY. THE DAILY DOSE FOR AVERAGE ADULT HUMAN IS 10-40 MILLIGRAMMES

ALLOMETRIC SCALING IS AN EMPIRICAL EXAMINATION OF THE RELATIONSHIP BETWEEN THE PHARMACOKINETIC PARAMETERS AND SIZE (USUALLY BODY WEIGHT, RATIO OF ORGAN & BODY WEIGHT, BREATHING NUMBER ETC). THE ALLOMETRIC EQUATION IS:

$$\frac{P}{BW} = a(BW)^m$$

WHERE P = PHYSIOLOGICAL PROPERTY OR ANATOMIC SIZE

a = EMPIRICAL COEFFICIENT

BW = BODYWEIGHT

m = ALLOMETRIC EXPONENT

THE SURFACE AREA STILL FINDS WIDE ACCEPTANCE IN THE CLINICAL LITERATURE, AND IS AT NO MORE THAN A ROUGH EMPIRICAL APPROXIMATION EVEN FOR HOMOITHERMS.

BODY SURFACE AREA (BSA) IS EQUAL TO: BODY WEIGHT (kg)$^{2/3}$ x 10^{-4} x K

K FOR DOG = 10.1

K FOR CAT = 10.0

EMPIRICAL COEFFICIENT = 10^{-4}

THE BODY WEIGHT EXPONENTS $^{2/3}$ OR ¾ CAN BE USED

BUT ¾ EXPONENT GIVES A HIGHER DOSE THAN $^{2}/_{3}$, HENCE SHOULD NOT BE APPLIED

DOG*, CAT, MONKEY*, BABOON*, RABBIT*, MICRO-PIG, MINI-PIG, SQUIRREL MONKEY, MARMOSET, FERRET, GUINEA – PIG*, HARMSTER, RAT & MOUSE

HUMAN EQUIVALENT DOSE (HED) WHICH I
EQUAL TO ANIMAL DOSE (AD) MULTIPLIE
BY ANIMAL KM DIVIDED BY HUMAN KM WA
USED TO PROJECT THE THERAPEUTIC DOSI
OF PIROXICAM IN SEVEN (7) MONOGASTRI
ANIMALS.

$$HED = \frac{AD \; x \; AK_m}{HK_m}$$

WHEREAS KM FACTOR IS BODY WEIGHT
(KG) DIVIDED BY BODY SURFACE AREA (m

$$K_m = \frac{BW}{BSA}$$

HUMAN EQUIVALENT NO-OBSERVABLE ADVERSE EFFECT DOSES WHERE DETERMINED BY MULTIPLYING ANIMAL NO-OBSERVABLE ADVERSE EFFECT DOSE BY ANIMAL WEIGHT (AW) DIVIDED BY HUMAN WEIGHT (HW).

$$\mathbf{HENAED} = \frac{ANAED\ x\ A_w}{H_w}$$

TABLE: HUMAN-MONOGASTRIC ANIMAL EQUIVALEN DOSES OF PIROXICAM (20 MILLIGRAMMES)

S/No	Species	Body weight (kg)	BSA (m^2)	K_m Factor	Therapeutic Dose (mg)	Total Translated Dose (mg)	Total give Literature d (mg)
1.	Mouse	0.02	0.007	2.9	3.6	0.072*	
2.	Hamster	0.08	0.02	4.0	2.6	0.2*	
3.	Rat	0.15	0.025	6.0	1.7	0.25*	
4.	Guinea pig	0.4	0.069	5.8	1.8	0.72*	
5.	Rabbit	1.8	0.15	12.0	0.89	1.6	-
6.	Monkey	3.0	0.24	12.5	0.85	2.5	-
7.	Baboon	12	0.6	20.0	0.53	6.3	-
8.	Ferret	0.3	0.043	7.0	1.53	0.45*	
9.	Marmoset	0.35	0.06	5.8	1.84	0.64*	
10.	Squirrel monkey	0.6	0.09	6.7	1.59	0.95*	
11.	Cat	7.0	0.37	18.9	0.56	3.9*	-
12.	Dog*	10	0.5	20.0	0.53*	5.3*	3 – 5
13.	Micro-pig	20	0.74	27.0	0.39	7.8	-
14.	Mini-pig	40	1.14	35.1	0.30*	12**	-
15.	Adult human	70	1.86	37.6	0.285	-	10-40**

*SINGLE DOSES OF PIROXICAM (20 - 4
MG) IN HUMAN ARE REASONABLY
EFFECTIVE FOR TREATING MODERATE T
SEVERE POST-OPERATIVE PAINS AND
COMPARE FAVOURABLY WITH OPIOID
ANALGESICS SUCH AS
DEXTROPROPOXYPHENE AND TRAMADO
*FEW ADVERSE EFFECTS WERE REPORTI
AND PIROXICAM APPEARS TO BE FAIRL
TOLERATED IN THIS CLINICAL CONTEX

***IN MULTIPLE DOSING THE ADVERSE EFFECT PROFILE MAY BE MORE PROMINENT, THEREFORE, THERE IS A DEFINITE NEED TO BE ABLE TO QUANTITATIVELY ASSESS THE EFFICAC AND ADVERSE EFFECTS OF PIROXICAM IN PROLONGED DOSING REGIMENS (MOORE ET AL., 2010).**

THE EXTRAPOLATED HIGH DOSES OF PIROXICAM FOR MONOGASTRIC ANIMALS AGREES WITH THE REPORTS O CALEJESAN ET AL. (2000), SUKUMARANNAR ET AL. (2002) AND HELLYER ET AL. (2007) INDICATING THAT ANIMALS FEEL MORE PAIN THAN HUMANS, SINCE THEY POSSESS MORE DIFFUSE NEURAL NETWORKS.

THE EXTRAPOLATED DOSE OF PIROXICAM (1.7 MG/KG) AGREES WITH THE REPORT OF UDEGBUNAM ET AL. (2012) INDICATING THAT PIROXICAM (5MG/GK) ALLEVIATED PAIN AND STRESS ASSOCIATED WITH WOUNDS IN RATS WITH MINIMAL SIDE EFFECTS.

STURMAN AND SMITH (1967) REPORTED THAT RHESUS MONKEY, RABBIT AND GUINEA-PIG RESEMBLE MAN IN HAVING A RELATIVELY HIGH AFFINITY FOR BINDING SALICYTE A NSAIDS SIMILAR TO PIROXICAM IN PHARMACOLOGICAL ACTION. BUT BABOON, DOG, RAT AND MOUSE HAD A LOW BINDING CAPACITY.

GASTRIC LESION AND RENAL PAPILLAR
NECROSIS HAVE OCCURRED IN DOGS
RECEIVING 1 MG/KG DAILY (GALBRAIT
AND MCKELLAR, 1991; KNAPP ET AL.,
1992). HOWEVER, LITTLE EVIDENCE O
TOXICITY (GASTROINTESTINAL BLEEDI
WAS NOTED AFTER ADMINISTRATION C
0.3 MG/KG EVERY OTHER DAY
(GALBRAITH AND MCKELLAR, 1991;
KNAPP ET AL., 1992).

EXTRAPOLATION FROM USE IN HUMANS TO DOGS SHOULD BE DONE CAUTIOUSLY BECAUSE OF POSSIBLE DIFFERENCES IN VOLUME OF DISTRIBUTION, THERAPEUTIC CONCENTRATIONS OR SAFETY MARGIN (BOOTHE, 2001).

CONCLUSION:

i. THE EXTRAPOLATED TOTAL DOSES FOR DOG (10kg), CAT (7kg), RABBIT (1.8kg), MONKEY (3kg), BABOON (6.3kg), MICRO-PIG (20kg) AND MINI-PIG (40kg) ARE 5.3, 3.9, 1.6 2.5, 6.3, 1.6mg RESPECTIVELY
ii. LITERATURE SEARCH HAS SHOWN A TOTAL OF 3-5mg FOR DOG WEIGHING 10kg
iii. FOR A DOG WEIGHING 10kg, A DOSE OF 5.3 MILLIGRAMM SHOULD NOT BE EXCEEDED, AND THE SAME PRINCIPLE APPLIES TO THE REST OF EXTRAPOLATED DOSES, SINCE THE DOSES HAVE NOT BEEN EVALUATED
iv. LABORATORY TEST CAN BE CARRIED OUT FOR VALIDATIO OF THE EXTRAPOLATED DOSES.
v. THE ROUGH ESTIMATION OF THERAPEUTIC DOSES FOR HUMAN DRUGS WHOSE ANIMAL DOSES HAVE NOT BEEN DETERMINED IS EVIDENT IN VETERINARY CLINICAL PRACTICE.

REFERENCES:

BOOTHE, 2001 CALEJESAN ET AL., 2000

DUBOIS & DUBOIS, 1915, 1916

GALBRATH AND MCKELLAR, 1991

HELLYER ET AL. 2007

MOORE ET AL., 2010

PLUNKETT, 2001, KAPP ET AL., 1992, 1994

REFERENCES:

REAGAN-SHAW ET AL., 2007

SAGANUWAN, 2012

SAGANUWAN & ONYEYILI, 2014

STURMAN AND SMITH, 1967

SUKUMARANNAR ET AL., 2002

UDEGBUNA, ET AL., 2012

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