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

SAGANUWAN ALHAJI SAGANUWAN (DVM, PGD, PGDE, MSc, PhD, FIIA)
PIROXICAM IS A NON-STEROIDAL ANTI-INFLAMMATORY ANALGESIC THAT CAN CAUSE ALTERATION 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) \(^{2/3}\) \times 10^{-4} \times K

K FOR DOG = 10.1
K FOR CAT = 10.0

EMPIRICAL COEFFICIENT = 10^{-4}

THE BODY WEIGHT EXPONENTS \(\frac{2}{3}\) OR \(\frac{3}{4}\) CAN BE USED
BUT $\frac{3}{4}$ EXPONENT GIVES A HIGHER DOSE THAN $\frac{2}{3}$, 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 IS EQUAL TO ANIMAL DOSE (AD) MULTIPLIED BY ANIMAL KM DIVIDED BY HUMAN KM WAS USED TO PROJECT THE THERAPEUTIC DOSE OF PIROXICAM IN SEVEN (7) MONOGASTRIC ANIMALS.

\[ HED = \frac{AD \times AK_m}{HK_m} \]

WHEREAS KM FACTOR IS BODY WEIGHT (KG) DIVIDED BY BODY SURFACE AREA (m²).

\[ K_m = \frac{BW}{BSA} \]
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).

\[ \text{HENAED} = \frac{\text{ANAED} \times \text{AW}}{\text{HW}} \]
<table>
<thead>
<tr>
<th>S/No</th>
<th>Species</th>
<th>Body weight (kg)</th>
<th>BSA (m²)</th>
<th>K&lt;sub&gt;m&lt;/sub&gt; Factor</th>
<th>Therapeutic Dose (mg)</th>
<th>Total Translated Dose (mg)</th>
<th>Total given Literature dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Mouse</td>
<td>0.02</td>
<td>0.007</td>
<td>2.9</td>
<td>3.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Hamster</td>
<td>0.08</td>
<td>0.02</td>
<td>4.0</td>
<td>2.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Rat</td>
<td>0.15</td>
<td>0.025</td>
<td>6.0</td>
<td>1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Guinea pig</td>
<td>0.4</td>
<td>0.069</td>
<td>5.8</td>
<td>1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Rabbit</td>
<td>1.8</td>
<td>0.15</td>
<td>12.0</td>
<td>0.89</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Monkey</td>
<td>3.0</td>
<td>0.24</td>
<td>12.5</td>
<td>0.85</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Baboon</td>
<td>12</td>
<td>0.6</td>
<td>20.0</td>
<td>0.53</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Ferret</td>
<td>0.3</td>
<td>0.043</td>
<td>7.0</td>
<td>1.53</td>
<td>0.45*</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>Marmoset</td>
<td>0.35</td>
<td>0.06</td>
<td>5.8</td>
<td>1.84</td>
<td>0.64*</td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>Squirrel monkey</td>
<td>0.6</td>
<td>0.09</td>
<td>6.7</td>
<td>1.59</td>
<td>0.95*</td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>Cat</td>
<td>7.0</td>
<td>0.37</td>
<td>18.9</td>
<td>0.56</td>
<td>3.9*</td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>Dog*</td>
<td>10</td>
<td>0.5</td>
<td>20.0</td>
<td>0.53*</td>
<td>5.3*</td>
<td>3–5</td>
</tr>
<tr>
<td>13.</td>
<td>Micro-pig</td>
<td>20</td>
<td>0.74</td>
<td>27.0</td>
<td>0.39</td>
<td>7.8</td>
<td></td>
</tr>
<tr>
<td>14.</td>
<td>Mini-pig</td>
<td>40</td>
<td>1.14</td>
<td>35.1</td>
<td>0.30*</td>
<td>12**</td>
<td></td>
</tr>
<tr>
<td>15.</td>
<td>Adult human</td>
<td>70</td>
<td>1.86</td>
<td>37.6</td>
<td>0.285</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SINGLE DOSES OF PIROXICAM (20 - 40 MG) IN HUMAN ARE REASONABLY EFFECTIVE FOR TREATING MODERATE TO SEVERE POST-OPERATIVE PAINS AND COMPARE FAVOURABLY WITH OPIOID ANALGESICS SUCH AS DEXTROPROPOXYPHENE AND TRAMADOL. FEW ADVERSE EFFECTS WERE REPORTED AND PIROXICAM APPEARS TO BE FAIRLY TOLERATED IN THIS CLINICAL CONTEXT.
*IN MULTIPLE DOSING THE ADVERSE EFFECT PROFILE MAY BE MORE PROMINENT, THEREFORE, THERE IS A DEFINITE NEED TO BE ABLE TO QUANTITATIVELY ASSESS THE EFFICACY AND ADVERSE EFFECTS OF PIROXICAM IN PROLONGED DOSING REGIMENS (MOORE ET AL., 2010).
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 NSAIDs similar to piroxicam in pharmacological action. But baboon, dog, rat and mouse had a low binding capacity.
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 A DOG WEIGHING 10kg

iii. FOR A DOG WEIGHING 10kg, A DOSE OF 5.3 MILLIGRAMMES SHOULD NOT BE EXCEEDED, AND THE SAME PRINCIPLE APPLIES TO THE REST OF EXTRAPOLATED DOSES, SINCE THE DOSES HAVE NOT BEEN EVALUATED N BE CARRIED OUT FOR VALIDATION OF THE EXTRAPOLATED DOSES.

iv. LABORATORY TEST CAN BE CARRIED OUT FOR VALIDATION 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
REFERENCES:

REAGAN-SHAW ET AL., 2007
SAGANUWAN, 2012
SAGANUWAN & ONYEYILI, 2014
STURMAN AND SMITH, 1967
SUHKUMARANNAR ET AL., 2002
UDEGBUNA, ET AL., 2012
ACKNOWLEDGEMENT

I SINCERELY THANK THE MANAGEMENT OF THE OMIC FOR GIVING ME AN OPPORTUNITY TO PRESENT THIS FOR THE SAKE OF KNOWLEDGE, OUR CLIENTS AND PATIENTS.
THANKS FOR LISTENING