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New use of indomethacin

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Indomethacin in ground pellet mixture was fed to a group of starved albino mice 6-8 weeks old, weighing 20-26 g in varying concentrations ranging from 0.0125–1.0 % w/w. The mice were observed for signs of toxicity over a period of 8 days or until death and the LD_{100} determined. The same LD_{100} indomethacin concentration was fed to a group of albino rats to determine if the results could be replicated in a different rodent species. All the mice fed concentrations of indomethacin ranging from 0.0625–1.0% died within 3 days and none died within 24 h. These results were replicated in rats but in this case, death occurred within 6 days. The LD_{100} indomethacin dose in mice was 35 mg/kg body weight compared to 65mg/kg given in literature for Zinc Phosphide. Most prominent manifestation of toxicity at death was extensive haemorrhage in gastrointestinal tract. Blood clotting time just before death was over 30 minutes compared to that of control mice which was 10-15 sec. Zinc phosphide, flocoumafen, difethiolone and bromadiolone, all established rodenticides in the Kenya market were fed to mice for purposes of comparison and their rodenticidal effects confirmed. On the basis of these results use of indomethacin as rodenticide is justified as it is much cheaper, readily available and safer in humans compared to other rodenticides in the market.

Key words: Indomethacin, rodenticide.

INTRODUCTION

Indomethacin, a non-selective cyclooxygenase inhibitor is one of the most prescribed non-steroidal anti-inflammatory drugs (NSAID) for relieving pain. It is cheap and the side defects are relatively mild compared to other NSAIDs. In the course of gathering information on NSAIDs use in Kenya, the authors found that indomethacin was being used as a rat poison and was claimed to be more effective than other rodenticides in the market. A literature survey revealed that indomethacin was also used informally as a rodenticide in some West African countries [1-4].

There is no patent on indomethacin use alone as a rodenticide. However, one patent application on rodenticide mixture is pending [5]. The patent relates to a mixture of biocide, pain killer (indomethacin included) and a rodenticide in specified percentage range. Forson *et al.* [1] have investigated the efficacy of indomethacin as rodenticide and compared it with Baraki®, a formulation product of second generation anticoagulant, difethialone.

In the present work, the authors have investigated the rodenticidal efficacy of indomethacin in mice and rats and compared it with zinc phosphide, flocoumafen, difethiolone and bromadiolone. The four reference rodenticides are used in Kenya and other parts of the world.

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EXPERIMENTAL

Experimental mice 6-8 weeks old and weighing 20-26 g were obtained from University of Nairobi, School of Pharmacy Animal House. The mean weight (±SD) was 22 g (2.4). In the first part of the experiment the aim was to determine the toxic effect profile by varying the amount of indomethacin incorporated in ground mice pellets. Indomethacin capsules (25 mg) used in this experiment were manufactured by Cosmos Pharmaceuticals (Nairobi, Kenya). The indomethacin capsules were purchased from a retail outlet and subjected to quality analysis as set out in the British Pharmacopoeia (BP) to verify the label claim with respect to indomethacin content. The capsules passed the BP test, the amount of indomethacin being 25 ± 1.2 mg.

Sixty six mice (33 males, 33 females) were starved for 24 h prior to experiment. They were then divided into 11 randomised groups of six mice (each 3 males and 3 females) and fed on a mixture of indomethacin/ground pellets in varying concentrations for 12 h. Details of indomethacin concentrations are given in table 1. After 12 h of feeding, the indomethacin/pellet mixture was replaced with normal mice pellets. Throughout the experiment water was provided *ad libitum*. The mice were observed throughout the experiment and any behavioural change or sign of toxicity noted. The mice that died were dissected and any macroscopic changes especially in the gastrointestinal tract (GIT) noted. The blood clotting time of a few mice was determined just before death. This was done by sacrificing the mouse by cervical dislocation, then cutting the neck and dipping a glass capillary tube into the blood from the jugular vein and then tilting the capillary tube repeatedly until the movement of blood in the tubes stopped.

From the above experiment it was possible to determine the indomethacin concentration which consistently gave 100% mortality (LD_{100}). As a follow-up, the experiment was repeated but in this case the mice were fed indomethacin mixture corresponding to LD_{100} (see group 6B Table 1) for 36 h instead of 12 h. Similarly this indomethacin mixture was fed to a group of six rats aged 8-10 weeks and weighing 200-240 g to determine if the results obtained with mice could be replicated in rats. The experimental details regarding the rats was exactly the same as that described for mice, the feeding period being 12 h in one group and 36 h in two others. A fourth group was fed difethiolone (Baraki®). Results are shown in table 2.

In the second part of the experiment, a group of mice aged 6-8 weeks weighing 20-26 g were starved for 24 h, then divided into 6 groups (M_1, M_2, M_3, M_4, M_5 and M_6) each with 6 mice. They were fed different types of rodenticides for 12 h as indicated in Table 3. Thereafter, the mice were fed on mice pellets for the remaining duration of the experiment. During the experiment, water was provided *ad libitum*. The mice were observed for behavioural change and signs of toxicity. Blood clotting time for a few mice in each group was determined just before death using glass capillary tube method described earlier.

RESULTS

Table 1 shows results obtained when mice starved for 24 h were fed varying ratios of indomethacin–pellet mixture. For mice fed 0.0625% w/w indomethacin and which consistently gave 100% mortality, two groups of mice are included. In one group (6A) mice were fed the test mixture for 12 h while the other group (6B) were fed the same mixture for 36 h. On the first day of the experiment, the starved mice consumed the mixture voraciously. In the second day experimental mice looked dull and progressively became sluggish and anorexic. There was no significant difference in mice fed indomethacin mixture for 12 h and 36 h and the latter group consumed very little after the first day. For mice that died there was extensive gastrointestinal haemorrhage. There was also blood and fluid in the peritoneal cavity. Blood was also noted in the anal region. The same result was observed in rats fed indomethacin–pellet mixture, which gave LD_{100} (Table 2). The blood clotting time determined just before mice died was more than 30 min, compared to 10-15 sec for the control group.

Table 1: Mice deaths as a function of indomethacin concentration ingested

Group	Indomethacin (% w/w)	Number of mice alive/number of mice dead								
		Day								
		0	1	2	3	4	5	6	7	8
1	1.0 (50/5)	6/0	6/0	5/6	1/6	0/6				
2	0.5 (25/5)	6/0	6/0	6/0	2/6	0/6	-	-	-	-
3	0.25 (25/10)	6/0	6/0	6/0	2/6	0/6	-	-	-	-
4	0.125(25/20)	6/0	6/0	6/0	3/6	0/6	-	-	-	-
5	0.085 (25/30)	6/0	6/0	6/0	3/6	0/6	-	-	-	-
6A	0.0625(25/30)	6/0	6/0	6/0	3/6	0/6	-	-	-	-
6B	0.0625(25/40)	6/0	6/0	6/0	4/6	2/6	0/6	-	-	-
7	0.0425 (25/60)	6/0	6/0	6/0	2/6	3/6	2/6	2/6	1/6	1/6
8	0.0312 (25/80)	6/0	6/0	6/0	6/0	3/6	3/6	3/6	3/6	3/6
9	0.025 (25/100)	6/0	6/0	6/0	6/0	5/6	5/6	5/6	5/6	5/6
10	0.0125 (25/200)	6/0	6/0	6/0	6/0	6/0	6/0	6/0	6/0	6/0
11	Control (pellet alone)	6/0	6/0	6/0	6/0	6/0	6/0	6/0	6/0	6/0

Parentheses = indomethacin, mg/ground pellets, g

Table 2: Rats death recorded over a period of 8 days, expressed as number alive/total number of experimental rats.

	Day								
	0	1	2	3	4	5	6	7	8
Group R_1	6/0	6/6	6/6	5/6	2/6	0/6	-	-	-
Group R_2	6/0	6/0	6/0	4/6	3/6	2/6	1/5	0/6	-
Group R_3	6/0	6/0	5/6	2/6	3/6	3/6	2/6	0/6	-
Group R_4	6/0	5/6	5/6	4/6	4/6	2/6	2/6	0/6	-

R_1 and R_2 -Rats fed indomethacin 0.0625% w/w for 36 h, R_3 - Rats fed indomethacin 0.0625% w/w for 12 h, R_4 -Rats fed difethiolone (Baraki®) Cake formulation (0.0025%)

In the second part of the experiment mice fed indomethacin mixture and four other rodenticides were observed and results are shown in Table 3. For group M_2, the concentration of zinc phosphide used had been shown by Maitai *et al.* [6] to give 100% mortality and death occurred within 24 h. For some, death occurred in less than 12 h. For the other 3 *super-warfarin* anticoagulants (difethiolone, flocoumafen and bromadiolone) mice in group M_3, M_4 and M_5 showed no signs of toxicity up to the last hour before death. They were feeding normally on mice pellets. The blood clotting time determined immediately after death was more than 2 h. This means the experiment to determine the clotting time was discontinued after 2 h.

DISCUSSION

The rodenticidal effect of indomethacin is confirmed in the present experiment and therefore justified its informal use in Kenya. The rodenticidal effect of zinc phosphide and the third generation anticoagulants popularly referred to as *super-warfarin* is well documented in literature. The inclusion in the present experiment was for comparative purposes only. Taiwo *et al.* [2] have given a detailed description of the pathogenesis and pathology of indomethacin in albino mice.

Table 3: Mice dying over a period of 8 days expressed as number of mice alive/number of mice dead

Group	Rodenticide concentration (0.15% w/w)	Day								
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
M_1	0.625	6/0	6/0	6/0	3/6	0/6	-	-	-	-
M_2	0.15	6/0	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
M_3	0.005	6/0	6/0	6/0	1/5	1/6	0/6	0/6	0/6	0/6
M_4	0.005	6/0	6/0	6/0	5/6	4/6	0/6	0/6	0/6	0/6
M_5	0.0025	6/0	6/0	6/0	4/6	3/6	2/6	0/6	0/6	0/6
M_6	Control	6/0	6/0	6/0	6/0	6/0	6/0	6/0	6/0	6/0

M_1-Indomethacin, M_2-zinc phosphide, M_3-flocoumafen, M_4-bromadialone, M_5-difethialone, M_6-control (pellets).

They have described symptoms of poisoning and detailed post-mortem findings. The most prominent feature of poisoning with indomethacin is extensive haemorrhage in the gastrointestinal tract, a fact confirmed in the present work. Nonsteroidal anti-inflammatory drugs like indomethacin are known antiplatelet agents and would be expected to prolong the blood clotting time, a fact confirmed in the present work. This observation has not been reported before. In the previous work by Maitai *et al.* [6] it was established that the amount of ground mice pellets consumed by each mouse (average weight 22g) after being starved for 24 h is 1.25 g. The amount of indomethacin in this mixture (25 mg/40g) consumed by each mouse is calculated as 0.7 mg. On this basis the LD_{100} for indomethacin is 35mg/kg. This is much lower than that of zinc phosphide given as 60-75mg/kg by Maitai *et al.* [6] as earlier described. On this basis indomethacin is a more potent rodenticide than zinc phosphide. However, zinc phosphide kills much faster than indomethacin. The amount of indomethacin used informally to kill rats is much higher than was used in the present experiment and is in the range of 5 capsules (total 125 mg) per 45 grammes (3 tablespoonfuls) of wheat/ maize flour [7]. This obviously represents an “overkill”.

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